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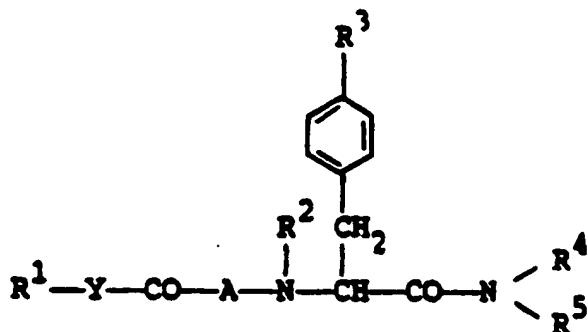
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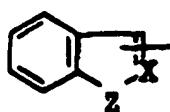
54 Peptide compounds, process for preparation thereof and pharmaceutical composition comprising the same.

55 A compound of the formula :



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wherein R¹ is lower alkyl, aryl, arylamino, pyridyl, pyrrolyl, pyrazolopyridyl, quinolyl, or a group of the formula :



wherein the symbol of a line and dotted line is a single bond or a double bond,
X is CH or N, and

Z is O, S or NH,
each of which may have suitable substituent(s);
R² is hydrogen or lower alkyl;
R³ is hydrogen or hydroxy;
R⁴ is lower alkyl which may have suitable substituent(s), and
R⁵ is ar(lower)alkyl which may have suitable substituent(s) or pyridyl(lower)alkyl, or
R⁴ and R⁵ are linked together to form benzene-condensed lower alkylene;
A is an amino acid residue excepting D-Trp, which may have suitable substituent(s); and
Y is bond, lower alkylene or lower alkenylene,
and a pharmaceutically acceptable salt thereof,
processes for their preparation and pharmaceutical compositions comprising them as active ingredient in
association with a pharmaceutically acceptable carrier or excipient.

PEPTIDE COMPOUNDS, PROCESSES FOR PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

The present invention relates to new peptide compounds and pharmaceutically acceptable salt thereof.

More particularly, it relates to new peptide compounds and pharmaceutically acceptable salts thereof which have pharmacological activities such as tachykinin antagonism, especially substance P antagonism, neurokinin A antagonism, neurokinin B antagonism, and the like, to processes for preparation thereof, to pharmaceutical composition comprising the same, and to a use of the same as a medicament.

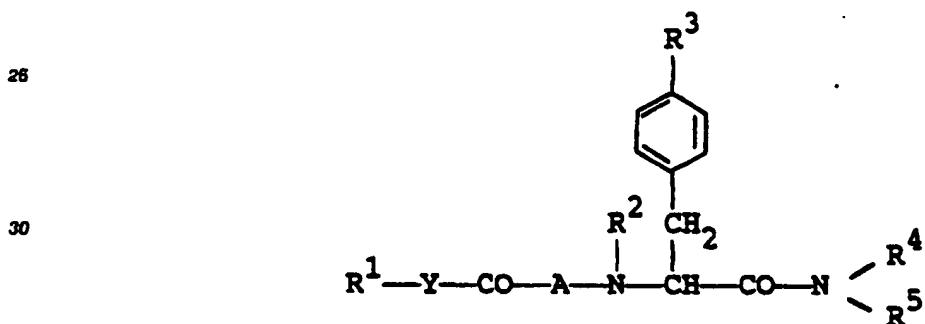
5 One object of the present invention is to provide new and useful peptide compounds and pharmaceutically acceptable salts thereof which have pharmacological activities such as tachykinin antagonism, especially substance P antagonism, neurokinin A antagonism, neurokinin B antagonism, and the like.

10 Another object of the present invention is to provide processes for the preparation of said peptide compounds and salts thereof.

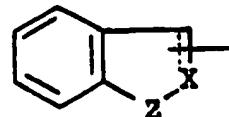
15 A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said peptide compounds and pharmaceutically acceptable salts thereof.

20 Still further object of the present invention is to provide a use of said peptide compound or a pharmaceutically acceptable salt thereof as tachykinin antagonist, especially substance P antagonist, neurokinin A antagonist or neurokinin B antagonist, useful for treating or preventing tachykinin mediated diseases, for example, respiratory diseases such as asthma, rhinitis, cough, expectoration, and the like; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, and the like; pains or aches (e.g., migraine, headache, toothache, cancerous pain, etc.); and the like in human being or animals.

25 The object compounds of the present invention can be represented by the following general formula (I).



36 wherein R¹ is lower alkyl, aryl, arylamino, pyridyl, pyrrolyl, pyrazolopyridyl, quinolyl, or a group of the formula :



45 wherein the symbol of a line and dotted line is a single bond or a double bond,
X is CH or N, and

Z is O, S or NH,

each of which may have suitable substituent(s);

R² is hydrogen or lower alkyl;

R³ is hydrogen or hydroxy;

50 R⁴ is lower alkyl which may have suitable substituent(s), and

R⁵ is ar(lower)alkyl which may have suitable substituent(s) or pyridyl(lower)alkyl, or

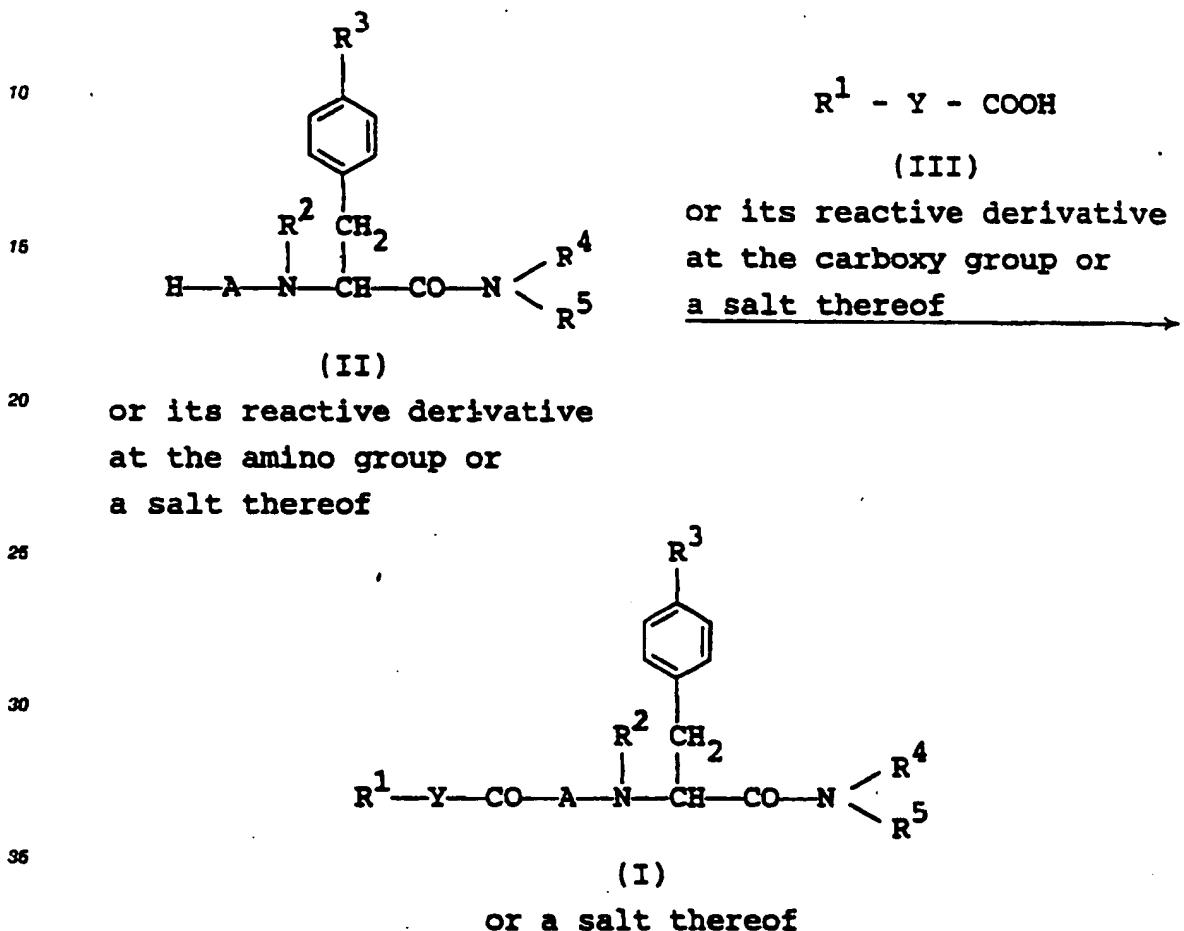
R⁴ and R⁵ are linked together to form benzene-condensed lower alkylene;

A is an amino acid residue excepting D-Trp, which may have suitable substituent(s); and

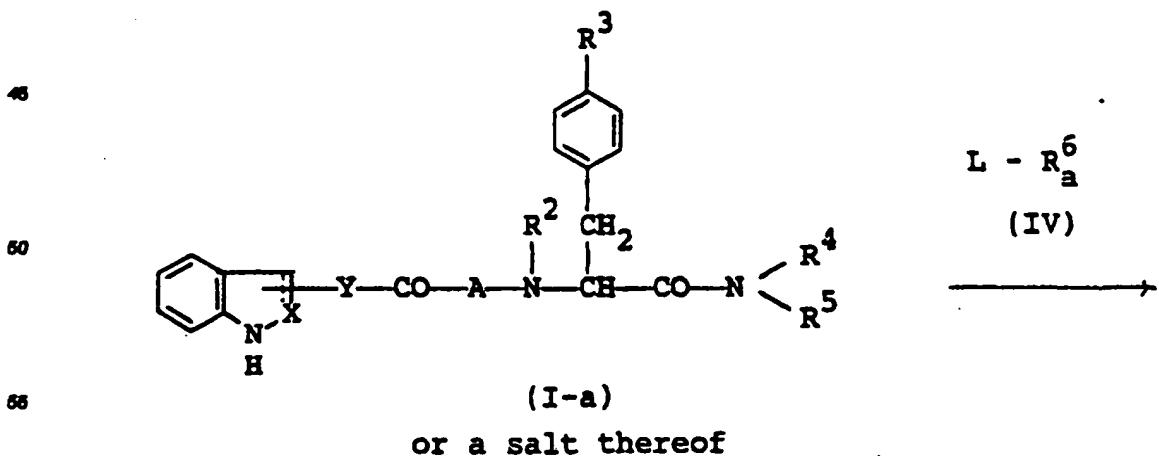
Y is bond, lower alkylene or lower alkenylene.

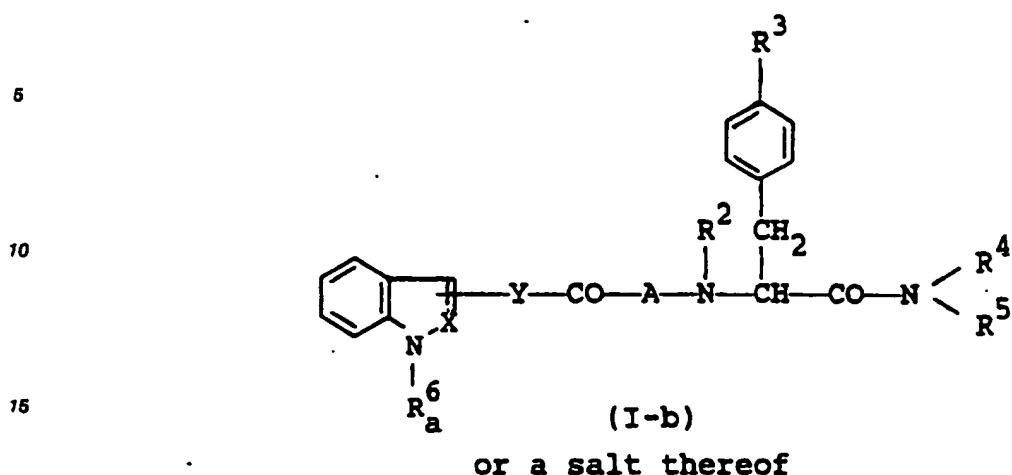
According to the present invention, the new peptide compounds (I) can be prepared by processes which are illustrated in the following schemes.

5 Process 1



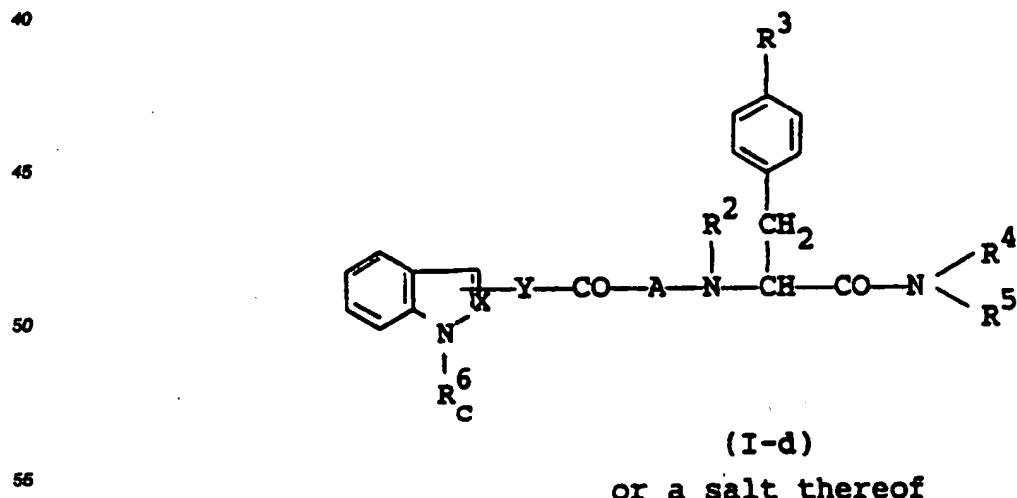
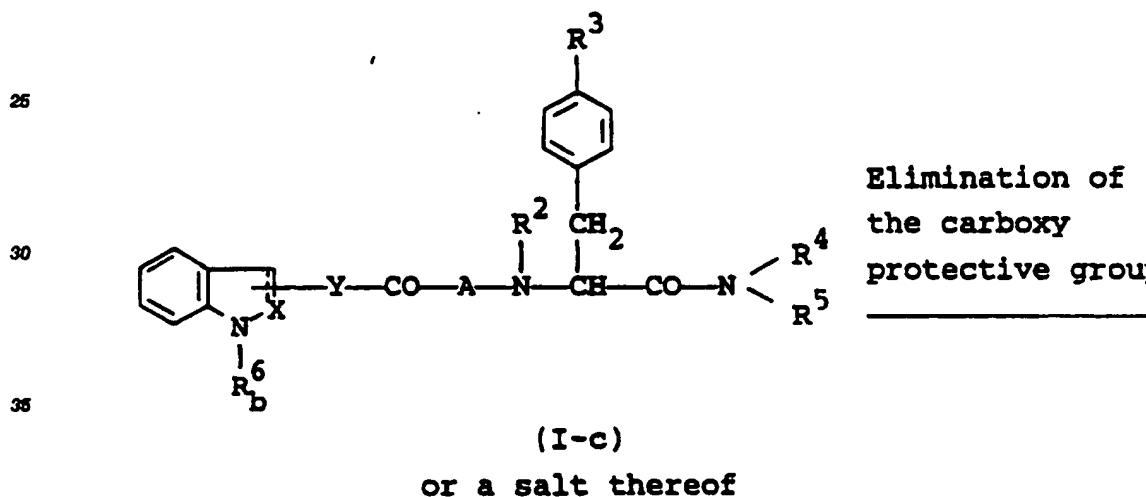
40 Process 2

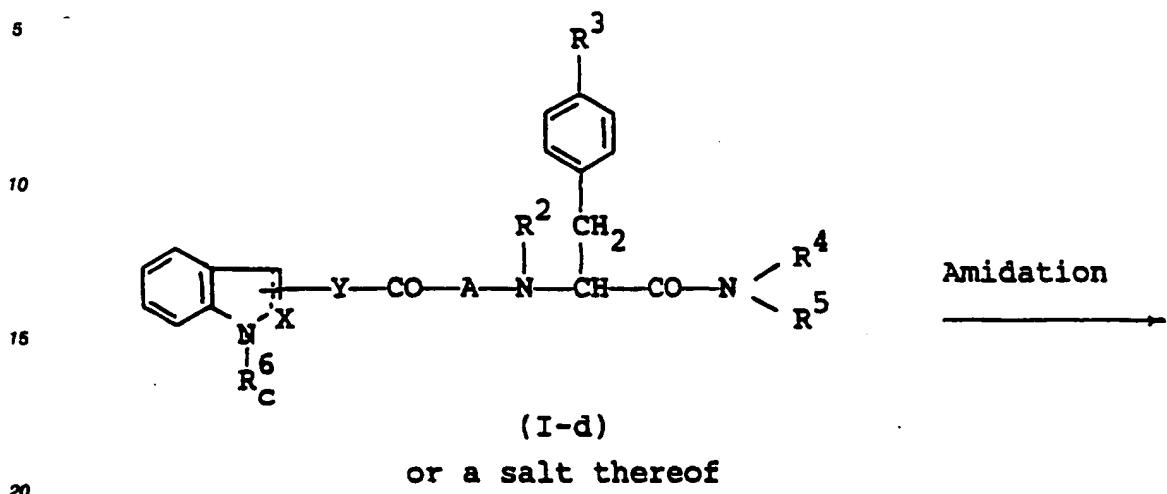


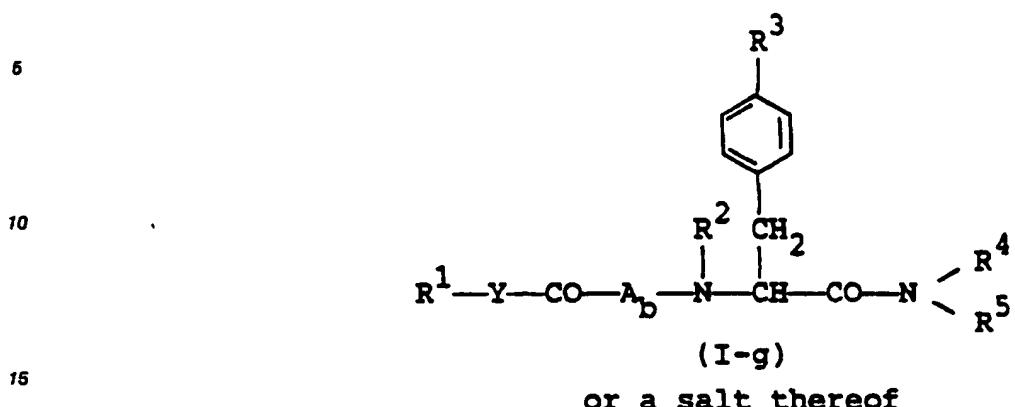


20 Process 3

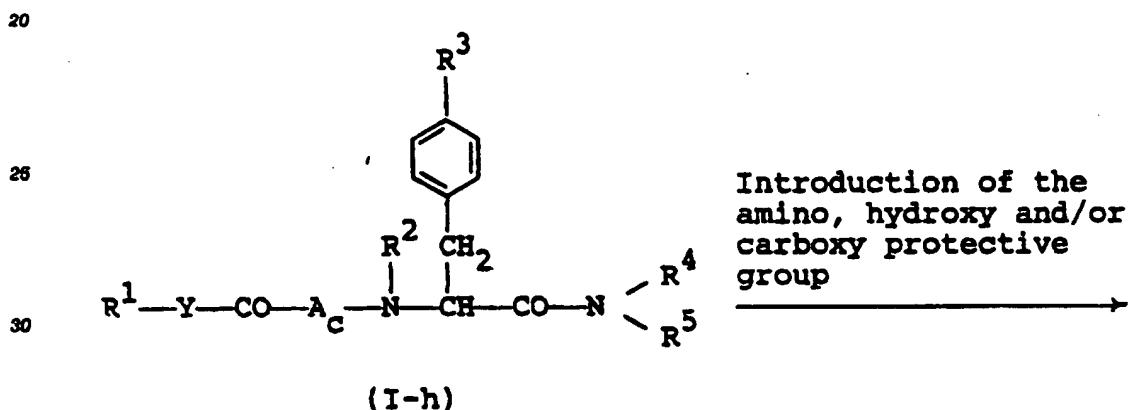
Elimination of
the carboxy
protective group



Process 4

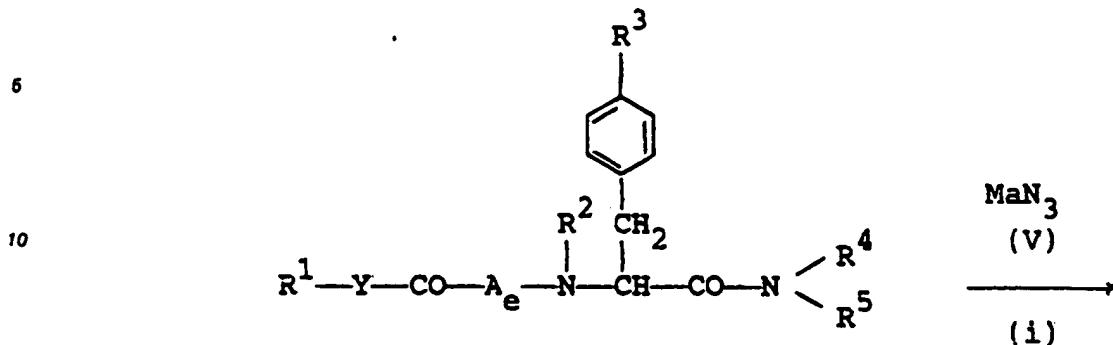


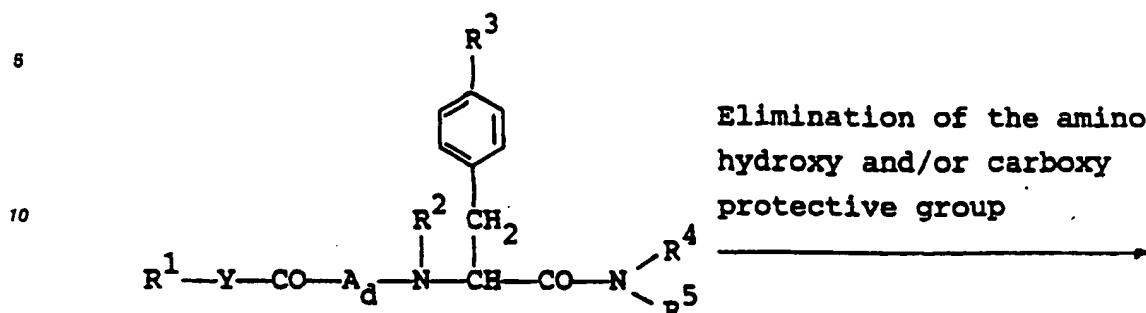
Process 6

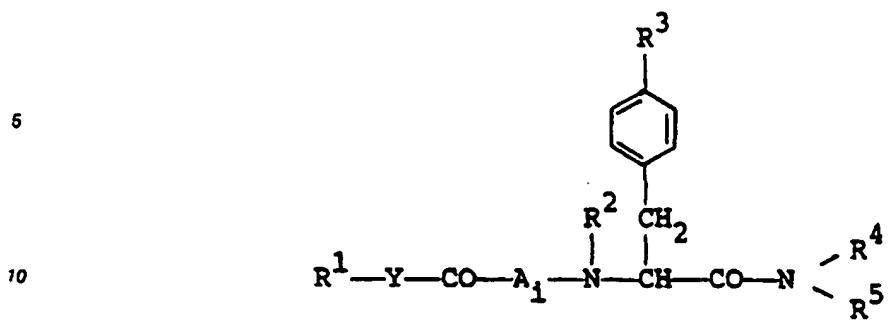


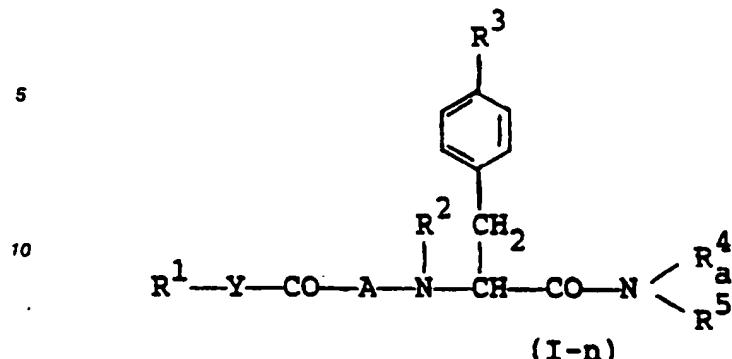
or its reactive derivative at the
 amino, hydroxy and/or carboxy group
 or a salt thereof

(I-i)
 or a salt thereof

Process 7

Process 8



Process 11

Suitable pharmaceutically acceptable salts of the starting and object compound are conventional non-toxic salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydriodide, sulfate, nitrate, phosphate, etc.), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnésium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4 carbon atom(s), unless otherwise indicated.

Suitable "lower alkyl" may include a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, in which the most preferred one is methyl.

Suitable "aryl" and the aryl moiety of "arylamino" may include phenyl, tolyl, xylol, mesityl, cumenyl, naphyl, and the like, in which the preferred one is C₆ -C₁₀ aryl and the most preferred one is phenyl.

Suitable "lower alkylene" is one having 1 to 6 carbon atom(s) and may include methylene, ethylene, trimethylene, propylene, tetramethylene, methyltrimethylene, hexamethylene, and the like, in which the preferred one is methylene, ethylene or trimethylene.

Suitable "lower alkenylene" is one having 2 to 6 carbon atom(s) and may include vinylene, propenylene, and the like, in which the preferred one is vinylene.

Suitable "an amino acid residue excepting D-Trp" means a bivalent residue derived from an amino acid excepting D-Trp, and such amino acid may be glycine (Gly), D- or L- alanine (Ala), β -alanine (β Ala), D- or L-valine (Val), D- or L- leucine (Leu), D- or L-isoleucine (Ile), D- or L- serine (Ser), D- or L- threonine (Thr), D- or L-cysteine (Cys), D- or L- methionine (Met), D- or L-phenylalanine (Phe), L-tryptophan (Trp), D- or L-tyrosine (Tyr), D- or L- proline (Pro), D- or L- hydroxyproline (Pro(OH)) such as 3-hydroxyproline (Pro-(3OH)) and 4-hydroxyproline (Pro(4OH)), D- or L- azetidine-2-carboxylic acid (Azt), D- or L- thioproline (Tpr), D- or L-aminoproline (Pro(NH₂)) such as 3-aminoproline (Pro(3NH₂)) and 4-aminoproline (Pro(4NH₂)), D- or L- pyroglutamic acid (pGlu), D- or L- 2-aminoisobutyric acid (Alb), D- or L-glutamic acid (Glu), D- or L- aspartic acid (Asp), D- or L- glutamine (Gln), D- or L- asparagine (Asn), D- or L-lysine (Lys), D- or L-arginine (Arg), D- or L- histidine (His), D- or L- ornithine (Orn), D- or L- hydroxypiperidinecarboxylic acid such as 5-hydroxypiperidine-2-carboxylic acid, D- or L- mercaptoproline (Pro(SH)) such as 3-mercaptoproline (Pro(3SH)) and 4-mercaptoproline (Pro(4SH)), whose side chains, which are amino, hydroxy, thiol or carboxy groups, may be substituted by the suitable substituent(s). Said suitable substituent(s) may include acyl such as carbamoyl, lower alkanoyl (e.g., formyl, acetyl, etc.), trihalo(lower)alkoxycarbonyl (e.g. 2,2,2-trichloroethoxycarbonyl, etc.), ar(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, etc.), lower alkylsulfonyl (e.g., mesyl ethylsulfonyl, etc.), lower alkoxaryl (e.g., methoxyaryl, ethoxyaryl, etc.), arylsulfonyl (e.g., phenylsulfonyl, tolylsulfonyl, etc.), haloar(lower)alkoxycarbonyl (e.g., o-chlorobenzylloxycarbonyl, etc.), carboxy(lower)alkanoyl (e.g., carboxyacetyl, carboxypropionyl, etc.), glycyl, β -alanyl, N-lower alkoxycarbonylglycyl (e.g., N-t-butoxycarbonylglycyl, etc.) and N-lower alkoxycarbonyl- β -alanyl (e.g., N-t-butoxycarbonyl- β -alanyl, etc.), N,N-di(lower)alkylamino(lower)alkanoyl (e.g., N,N-dimethylaminoacetyl, N,N-diethylaminoacetyl, N,N-dimethylaminopropionyl, N,N-diethylaminopropionyl, etc.), carboxyaryl, morpholinocarbonyl, amino(lower)alkanoyl (e.g., aminoacetyl, aminopropionyl, etc.), N-ar(lower)-alkoxycarbonylamino(lower)alkanoyl (e.g. N-benzyloxycarbonylaminoacetyl, etc.), threonyl, N-lower alkoxycarbonylthreonyl (e.g. N-t-butoxycarbonylthreonyl, etc.), N-lower alkanoylthreonyl (e.g. N-acetylthreonyl, etc.), N-lower alkoxycarbonyl(lower)alkyl-N-lower alkoxycarbonylamino(lower)alkanoyl (e.g. N-t-butoxycarbonylmethyl-N-t-butoxycarbonylaminoacetyl, etc.), α -glutamyl, N-ar(lower)alkoxycarbonyl-O-ar(lower)alkyl- α -glutamyl (e.g., N-benzyloxycarbonyl-O-benzyl- α -glutamyl, etc.), γ -glutamyl, N-ar(lower)-alkoxycarbonyl-O-ar(lower)alkyl- γ -glutamyl (e.g., N-benzyloxycarbonyl-O-benzyl- γ -glutamyl, etc.), lower alkyl (e.g., methyl, ethyl, t-butyl, etc.), carboxy(lower)alkyl (e.g. carboxymethyl, etc.), morpholino, glycino amide, threonino amide, N'-glutamino N-lower alkylamide (e.g., N'-glutamino N-t-butylamide, etc.), di(lower)-alkylamino (e.g. dimethylamino, etc.), ar(lower)alkyl (e.g. benzyl, phenethyl, etc.), trihalo(lower)alkyl (e.g. 2,2,2-trichloroethyl, etc.), lower alkoxycarbonyl(lower)alkyl (e.g., methoxycarbonylmethyl, ethoxycarbonylmethyl, t-butoxycarbonylmethyl, etc.), or usual protecting group used in the field of art. In case that such amino acid contain a thio, it may be its sulfoxide or sulfone.

Suitable "carboxy(lower)alkyl" may include carboxymethyl, carboxyethyl, carboxypropyl, and the like.

Suitable "protected carboxy(lower)alkyl" means the above-mentioned carboxy(lower)alkyl, in which the

carboxy group is protected by a conventional protective group such as esterified carboxy group. Preferred example of the ester moiety thereof may include lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, tert-butyl ester, etc.), and the like.

5 Suitable "carbamoyl(lower)alkyl" which may have suitable substituent(s)" may include carbamoyl(lower)-alkyl (e.g., carbamoylmethyl, carbamoylethyl, carbamoylpropyl, etc.), carbamoyl(lower)alkyl having suitable substituent(s) such as lower alkylcarbamoyl(lower)alkyl (e.g., methylcarbamoylmethyl, ethylcarbamoylmethyl, etc.), amino(lower)alkylcarbamoyl(lower)alkyl (e.g., aminomethylcarbamoylmethyl, aminoethylcarbamoylmethyl, etc.), lower alkylamino(lower)alkylcarbamoyl(lower)alkyl (e.g., dimethylaminomethylcarbamoylmethyl, dimethylaminoethylcarbamoylmethyl, etc.), and the like.

10 Suitable "lower alkyl which may have suitable substituent(s)" may include a conventional group, which is used in the field of art such as lower alkyl, carboxy(lower)alkyl, protected carboxy(lower)alkyl, carbamoyl(lower)alkyl which may have suitable substituent(s), each of which is as exemplified above, lower alkylamino(lower)alkyl (e.g. dimethylaminomethyl, dimethylaminoethyl, etc.), hydroxy(lower)alkyl (e.g., hydroxymethyl, hydroxyethyl, etc.), protected hydroxy(lower)alkyl such as acyloxy(lower)alkyl (e.g. acetoxyethyl, etc.) and the like.

15 Suitable "an amino acid residue containing a thio" means a bivalent residue derived from an amino acid containing a thio, and may include Tpr, Met, and the like.

20 Suitable "an amino acid residue containing a sulfinyl or sulfonyl" means a bivalent residue derived from an amino acid containing a sulfinyl or sulfonyl, and may include Tpr(O), Met(O), Tpr(O²), Met(O²), and the like.

Suitable "an amino acid residue containing an amino, a hydroxy and/or a carboxy" may include a bivalent residue of an amino acid such as Pro(4OH), Ser, Thr, Tyr, and the like.

25 Suitable "an amino acid residue containing a protected amino, a protected hydroxy and/or a protected carboxy" means the above-mentioned group, in which the amino, hydroxy and/or carboxy is protected by a conventional group used in the field of the art such as carbamoyl, lower alkylsulfonyl (e.g., mesyl, ethylsulfonyl, etc.), arylsulfonyl (e.g., phenylsulfonyl, tolylsulfonyl, etc.), lower alkoxy carbonyl(lower)alkyl (e.g., methoxycarbonylmethyl, ethoxycarbonylmethyl, etc.), and the like.

30 Suitable "an amino acid residue containing sulfonyloxy which has a suitable substituent" means a bivalent residue derived from an amino acid containing sulfonyloxy which has a suitable substituent, in which "sulfonyloxy which has a suitable substituent" may include lower alkylsulfonyloxy (e.g., methylsulfonyloxy, ethylsulfonyloxy, etc.), halo(lower)alkylsulfonyloxy (e.g., trifluoromethylsulfonyloxy, etc.), arylsulfonyloxy (e.g., phenylsulfonyloxy, tolylsulfonyloxy, etc.), and the like.

Suitable "an amino acid residue containing an azido" may include a bivalent residue of an amino acid such as Pro(4N₃), and the like.

35 Suitable "an amino acid residue containing an amino" may include a bivalent residue of an amino acid such as Pro(4NH₂), and the like.

Suitable "alkaline metal" may include sodium, potassium, and the like.

Suitable "an acid residue" may include halogen (e.g., fluoro, chloro, bromo, iodo), acyloxy (e.g., tosyoxy, mesytoxy, etc.), and the like.

40 Suitable "ar(lower)alkyl which may have suitable substituent(s)" may include a conventional group, which is used in the field of amino acid and peptide chemistry, such as ar(lower)alkyl (e.g. trityl, benzhydryl, benzyl, phenethyl, etc.), substituted ar(lower)alkyl (e.g., o-fluorobenzyl, m-fluorobenzyl, o-trifluoromethylbenzyl, etc.), and the like.

45 Suitable "pyridyl(lower)alkyl" may include 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, and the like.

Suitable group of the formula :



in which R⁴ and R⁵ are linked together to form benzene-condensed lower alkylene, may include 1-indolinyl, 56 2-isoindolinyl, 1,2,3,4-tetrahydroquinolin-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl, and the like.

Suitable "hydroxy(lower)alkyl" may include hydroxymethyl, hydroxyethyl, hydroxypropyl, and the like.

Suitable "protected hydroxy(lower)alkyl" means the above-mentioned hydroxy(lower)alkyl, in which the hydroxy group is protected by a conventional protective group such as acyl (e.g. acetyl, etc.), and may

include acyloxyethyl and the like.

Suitable "amino protective group" may be a conventional protective group, which is used in the field of amino acid and peptide chemistry, that is, may include acyl such as lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, etc.), lower alkoxy carbonyl (e.g. methoxy carbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, etc.), and the like.

Suitable "an amino acid residue containing lower alkylthio" means a bivalent residue of an amino acid containing lower alkylthio, in which lower alkylthio may include methylthio, ethylthio, and the like.

Suitable substituent on R¹ moiety may include a conventional group, which is used in the field of amino acid and peptide chemistry, such as lower alkyl which may have suitable substituent(s), amino protective group, each as defined above, hydroxy, halogen (e.g. fluoro, chloro, etc.), lower alkoxy (e.g. methoxy, butoxy, etc.), N,N-di(lower)alkylamino (e.g. dimethylamino, etc.), lower alkoxy carbonyl (e.g. methoxycarbonyl, t-butoxycarbonyl, etc.), and the like.

Particularly, the preferred embodiments of R¹, R², R³, R⁴, R⁵, A and Y are as follows.

R¹ is lower alkyl (e.g. isopentyl, etc.);

16 aryl which may have one or more, preferably one to three substituent(s) selected from hydroxy, lower alkoxy and N,N-di(lower)alkylamino (e.g. phenyl, hydroxyphenyl, dihydroxyphenyl, hydroxydimethoxyphenyl, N,N-dimethylaminophenyl, etc.);

arylamino (e.g. anilino, etc.);

pyridyl;

20 pyrrolyl;

pyrazolopyridyl;

quinolyl;

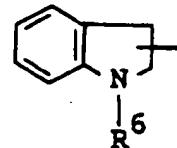
benzofuryl;

indazolyl;

25 benzothienyl;

a group of the formula :

30

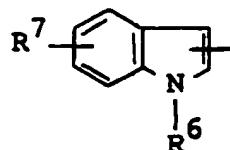


35 wherein R6 is hydrogen; or

lower alkoxy carbonyl (e.g. t-butoxycarbonyl, etc.);

or a group of the formula :

40



45

wherein R6 is hydrogen;

lower alkyl (e.g. methyl, isopropyl, etc.);

carboxy(lower)alkyl (e.g. carboxymethyl etc.);

esterified carboxy(lower)alkyl such as lower alkoxy carbonyl(lower)alkyl (e.g. t-butoxycarbonylmethyl, etc.);

50 N,N-di(lower)alkylamino(lower)alkyl (e.g. N,N-dimethylaminoethyl, etc.);

or

N,N-di(lower)alkylamino(lower)alkylcarbamoyl(lower)alkyl (e.g. N,N-dimethylaminoethylcarbamoylmethyl, etc.); and

R7 is hydrogen;

55 hydroxy;

halogen (e.g. chloro, etc.);

lower alkyl (e.g. methyl, etc.);

lower alkoxy (e.g. methoxy, etc.); or

N,N-di lower)alkylamino (e.g. N,N-dimethylamino, etc.);
 R² is hydrogen; or
 lower alkyl (e.g. methyl, etc.);
 R³ is hydrogen; or

5 hydroxy;
 R⁴ is lower alkyl (e.g. methyl, etc.);
 hydroxy(lower)alkyl (e.g. hydroxyethyl, etc.); or
 acyloxy(lower)alkyl such as lower alkanoyloxy(lower)alkyl (e.g. acetyloxyethyl, etc.);
 R⁵ is ar(lower)alkyl such as mono or di or triphenyl(lower)alkyl (e.g. benzyl, etc.);

10 haloar(lower)alkyl such as halo-substituted mono or di or triphenyl(lower)alkyl (e.g. fluorobenzyl, chlorobenzyl, etc.);
 halo(lower)alkylar(lower)alkyl such as halo(lower)alkyl-substituted mono or di or triphenyl(lower)alkyl (e.g. trifluoromethylbenzyl, etc.); or
 pyridyl(lower)alkyl (e.g. pyridylmethyl, etc.); or

15 R⁴ and R⁵ are linked together to form benzene-condensed lower alkylene (e.g. 1,2,3,4-tetrahydroquinolin-2-yl, etc.);
 A is a bivalent residue derived from an amino acid excepting D-Trp, which may have suitable substituent(s) such as proline, hydroxyproline (e.g. 4-hydroxyproline, etc.), glycine, serine, asparagine, aminoisobutyric acid (e.g. 2-aminoisobutyric acid, etc.), azetidinecarboxylic acid (e.g. azetidine-2-carboxylic acid, etc.),

20 thioproline, aspartic acid, lysine, methionine, threonine, alanine, ornithine, hydroxypiperidinecarboxylic acid (e.g. 5-hydroxypiperidine-2-carboxylic acid, etc.), 4-acyloxyproline [e.g. 4-lower alkanoyloxyproline, 4-lower alkanesulfonyloxyproline, 4-arenesulfonyloxyproline, 4-carbamoyloxyproline, etc.], 4-lower alkoxyproline, 4-carboxy(lower)alkoxyproline, 4-lower alkoxy carbonyl-lower alkoxyproline, 4-lower alkylthioproline, 4-aminoproline, 4-acylaminoproline [e.g. 4-carboxy(lower)alkanoylaminoproline, 4-amino(lower)-

25 alkanoylaminoproline, 4-ar(lower)alkoxycarbonylaminolower)alkanoylaminoproline, 4-amino and carboxy substituted lower alkanoylaminoproline, 4-ar(lower)alkoxycarbonylaminolower)alkanoylaminoproline and ar(lower)alkoxycarbonyl substituted lower alkanoylaminoproline, etc.], 4-oxaloaminoproline, 4-lower alkoxyalaminoproline, 4-lower alkanesulfonylaminoproline, 4-N,N-di(lower)alkylamino(lower)alkanoylaminoproline, etc.], O³-lower alkylserine, O³-ar(lower)alkylserine, thioproline sulfoxide, thioproline sulfone, O⁴-ar(lower)alkyl hydrogen aspartate, (carbamoyl and hydroxy substituted lower alkylamino)- β -aspartate, carbamoyl(lower)alkylamino- β -aspartate, morpholino- β -aspartate, (carbamoyl and lower alkylcarbamoyl substituted lower alkylamino)- β -aspartate, N⁶-acyllysine [e.g. N⁶-ar(lower)alkoxycarbonyllysine, N⁶-haloar(lower)alkoxycarbonyllysine, N⁶-N,N-di(lower)-alkylamino-lower alkanoyllysine, N⁶-morpholinocarbonyllysine, N⁶-N-lower alkoxy carbonyl-N-lower alkoxy carbonyl(lower)alkylamino(lower)alkanoyllysine, N⁶-(hydroxy and lower alkanoyl)amino substituted lower alkanoyl)lysine, N⁶-(hydroxy and lower alkoxy carbonyl)amino substituted lower alkanoyl)lysine, N⁶-lower alkoxy carbonyl amino(lower)alkanoyllysine, N⁶-amino lower)alkanoyllysine, etc.], N⁵-acylornithine [e.g. N⁵-ar(lower)alkoxycarbonylornithine, N⁵-(hydroxy and lower alkanoyl)amino substituted lower alkanoyl)ornithine, N⁵-(hydroxy and lower alkoxy carbonyl)amino substituted lower alkanoyl)ornithine, etc.], etc.; more preferably

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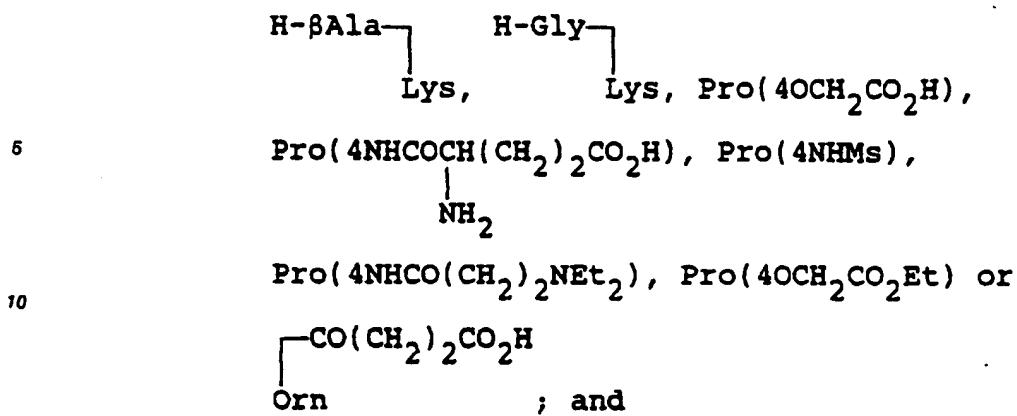
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15 Y is bond;
 lower alkylene (e.g. methylene, ethylene, trimethylene, etc.); or
 lower alkenylene (e.g. vinylene, etc.).
 20 The processes for preparing the object compound (I) are explained in detail in the following.

Process 1

25 The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the amino group or a salt thereof with the compound (III) or its reactive derivative at the carboxy group or a salt thereof.

30 Suitable reactive derivative at the amino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl) acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (II) with phosphorus trichloride or phosgene, and the like.

35 Suitable salts of the compound (II) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

40 Suitable reactive derivative at the carboxy group of the compound (III) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride within acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfuric acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethylaminomethyl [(CH₂)₂N=CH-] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenylthioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. 45 These reactive derivatives can optionally be selected from them according to the kind of the compound (III) to be used.

50 Suitable salts of the compound (III) and its reactive derivative may be a base salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.], an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.], or the like, and an acid addition salt as exemplified for the compound (I).

55 The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride,

tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (III) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinocarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride);

phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 2

26 The object compound (I-b) or a salt thereof can be prepared by reacting the compound (I-a) or a salt thereof with the compound (IV).

The present reaction is usually carried out in the presence of a base such as alkali lithium (e.g. n-butyl lithium, etc.), alkali metal hydride (e.g. sodium hydride, potassium hydride, etc.), tri(lower)alkylamine (e.g. trimethylamine, triethylamine, etc.), pyridine or its derivative (e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.), or the like.

The present reaction is usually carried out in a solvent such as dioxane, dimethyl sulfoxide, dimethylformamide, diethylformamide, dimethylacetamide, benzene, tetrahydrofuran, or any other solvent which does not adversely affect the reaction. In case that the base to be used is liquid, it can also be used as a solvent.

If necessary, the present reaction can be used phase transfer catalyst (e.g. cetyltrimethylammonium chloride, etc.).

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under heating.

The present reaction includes, within its scope, the case that the hydroxy group on A is reacted during the reaction or at the post-treating step of the present process.

40

Process 3

45 The object compound (I-d) or a salt thereof can be prepared by subjecting the compound (I-c) or a salt thereof to elimination reaction of the carboxy protective group.

In the present elimination reaction, all conventional methods used in the elimination reaction of the carboxy protective group, for example, hydrolysis, reduction, elimination using Lewis acid, etc. are applicable. When the carboxy protective group is an ester, it can be eliminated by hydrolysis or elimination using Lewis acid. The hydrolysis is preferably carried out in the presence of a base or an acid.

50 Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g. sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), or the like, and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-one, 1,4-diazabicyclo[2.2.2]octane, 1,5-

diazabicyclo[5.4.0]undecene-5 or the like. The hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.).

5 The present hydrolysis is usually carried out in an organic solvent, water, or a mixed solvent thereof.

The reaction temperature is not critical, and it may suitably be selected in accordance with the kind of the carboxyprotective group and the elimination method.

10 The elimination using Lewis acid is carried out by reacting the compound (I-c) or a salt thereof with Lewis acid such as boron trihalide (e.g. boron trichloride, boron trifluoride, etc.), titanium tetrahalide (e.g. titanium tetrachloride, titanium tetrabromide, etc.), tin tetrahalide (e.g. tin tetrachloride, tin tetrabromide, etc.), aluminum halide (e.g. aluminum chloride, aluminum bromide, etc.), trihaloacetic acid (e.g. trichloroacetic acid, trifluoroacetic acid, etc.) or the like. This elimination reaction is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol, etc.) and is usually carried out in a solvent such as nitroalkane (e.g. nitromethane, nitroethane, etc.), alkylene halide (e.g. methylene chloride, ethylene chloride, etc.), diethyl ether, carbon disulfide or any other solvent which does not adversely affect the reaction. These solvents may be used as a mixture thereof.

15 The reduction elimination can be applied preferably for elimination of the protective group such as halo-(lower)alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl, etc.) ester, ar(lower)alkyl (e.g. benzyl, etc.) ester or the like.

20 The reduction method applicable for the elimination reacting may include, for example, reduction by using a combination of a metal (e.g. zinc, zinc amalgam, etc.) or a salt of chromium compound (e.g. chromous chloride, chromous acetate, etc.) and an organic or an inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, etc.); and conventional catalytic reduction in the presence of a conventional metallic catalyst (e.g. palladium carbon, Raney nickel, etc.).

25 The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming.

The present elimination reaction includes, within its scope, the case that the amino, hydroxy and/or carboxy protective group for A is eliminated during the reaction or at the post-treating step of the present process.

30

Process 4

35 The object compound (I-e) or a salt thereof can be prepared by subjecting the compound (I-d) or its reactive derivative at the carboxy group or a salt thereof to amidation.

The amidating agent to be used in the present amidation may include amine which may have suitable substituent(s) such as lower alkyl (e.g., methyl, ethyl, etc.), amino(lower)alkyl (e.g., aminomethyl, aminoethyl, etc.), lower alkylamino(lower)alkyl (e.g., dimethylaminomethyl, dimethylaminoethyl, etc.) and the like.

40 Suitable reactive derivative at the carboxy group of the compound (I-d) can be referred to the ones as exemplified for the compound (III) in Process 1.

This reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. reaction derivatives, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1. Process 5

45 The object compound (I-g) or a salt thereof can be prepared by oxidizing the compound (I-f) or a salt thereof.

50 The oxidizing agent to be used in this reaction may include an inorganic peracid or a salt thereof (e.g. periodic acid, persulfuric acid, or sodium or potassium salt thereof, etc.), an organic peracid or a salt thereof (e.g. perbenzoic acid, m-chloroperbenzoic acid, performic acid, peracetic acid, chloroperacetic acid, trifluoroperacetic acid, or sodium or potassium salt thereof, etc.), ozone, hydrogen peroxide, urea-hydrogen peroxide, N-halosuccinimide (e.g. N-bromosuccinimide, N-chlorosuccinimide, etc.), hydrochlorite compound (e.g. tert-butyl hydrochlorite, etc.) permanganate (e.g. potassium permanganate, etc.), or any other conventional oxidizing agent which can oxidize a sulfhydryl group to a sulfonyl group.

55 The present reaction can also be carried out in the presence of a compound comprising Group Vb or Vib metal in the Periodic Table of elements, for example, tungstic acid, molybdic acid, vanadic acid, etc., or an alkali or an alkaline earth metal salt thereof.

The present oxidation reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, acetic acid, chloroform, methylene chloride, acetone, methanol,

ethanol or a mixture thereof.

The reaction temperature is not critical and the reaction is preferably carried out under cooling to at ambient temperature.

5

Process 6

The object compound (I-i) or a salt thereof can be prepared by subjecting the compound (I-h) or its reactive derivative at the amino, hydroxy and/or carboxy group or a salt thereof to introduction reaction of 10 the amino, hydroxy and/or carboxy protective group.

The reaction can be carried out in substantially the same manner as Process 1, and therefore the reaction mode and reaction conditions [e.g. solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 1.

The present reaction includes, within its scope, the case that the amino group on R¹ is reacted during 15 the reaction or at the post-treating step of the present process.

Process 7-(I)

20 The compound (VI) or a salt thereof can be prepared by reacting the compound (I-i) or a salt thereof with the compound (V).

The reaction is usually carried out in a conventional solvent such as dimethyl sulfoxide or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under warming to heating. 25

Process 7-(II)

30 The object compound (I-k) or a salt thereof can be prepared by subjecting the compound (VI) or a salt thereof to hydrogenation. This reaction is usually carried out in the presence of triphenylphosphine, palladium on carbon, or the like.

The reaction is usually carried out in a conventional solvent such as alcohol (e.g., methanol, ethanol, etc.), or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating. 35

Process 8

40 The object compound (I-h) or a salt thereof can be prepared by subjecting the compound (I-i) or a salt thereof to elimination reaction of the amino, hydroxy and/or carboxy protective group.

This reaction can be carried out in substantially the same manner as Process 3, and therefore the reaction mode and reaction conditions [e.g. bases, acids, reducing agents, catalysts, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 3.

The present elimination reaction includes, within its scope, the case that the carboxy protective group 45 for R¹ is eliminated during the reaction or at the post-treating step of the present process.

Process 9

50 The object compound (I-1) or a salt thereof can be prepared by reacting the compound (I-k) or a salt thereof with the compound (VI).

The reaction is usually carried out in a conventional solvent such as N,N-dimethylformamide or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating. 55

Process 10

The object compound (I-a) or a salt thereof can be prepared by subjecting the compound (I-m) or a salt thereof to elimination reaction of the amino, protective group.

This reaction can be carried out in substantially the same manner as Process 3, and therefore the reaction mode and reaction conditions [e.g. bases, acids, reducing agents, catalysts, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 3.

Process 11

10 The object compound (I-o) or a salt thereof can be prepared by subjecting the compound (I-n) or a salt thereof to elimination reaction of the hydroxy protective group.

This reaction can be carried out in substantially the same manner as Process 3, and therefore the reaction mode and reaction conditions [e.g. bases, acids, reducing agents, catalysts, solvents, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 3.

15 The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

20 The object compounds (I) and pharmaceutically acceptable salt thereof have pharmacological activities such as tachykinin antagonism, especially substance P antagonism, neurokinin A antagonism or neurokinin B antagonism, and therefore are useful for treating or preventing tachykinin mediated diseases, for example, respiratory diseases such as asthma, rhinitis, cough, expectoration, and the like; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, and the like; pains or aches (e.g. migraine, headache, toothache, cancerous pain, etc.); and the like.

25 Further, it is expected that the object compounds (I) of the present invention are useful for treating or preventing ophthalmic diseases such as glaucoma, uveitis, and the like; gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, food allergy, and the like; inflammatory diseases such as nephritis, and the like; circulatory diseases such as hypertension, angina pectoris, cardiac failure, thrombosis, and the like; pollakiuria; dementia; schizophrenia; Huntington's chorea; carcinoid syndrome; immunosuppressive agent; and the like.

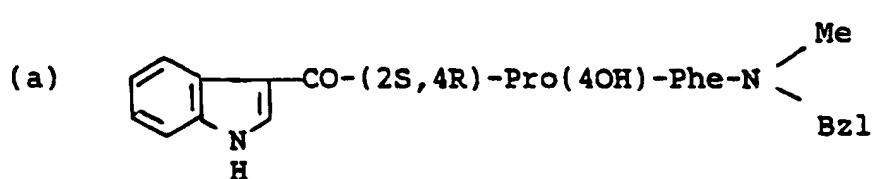
30 For therapeutic purpose, the compounds (I) and pharmaceutically acceptable salts thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension, emulsion, or the like. If desired, there may be included in these preparation, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

35 While the dosage of the compounds (I) will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating asthma and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

40 In order to illustrate the usefulness of the object compound (I), the pharmacological test data of some representative compounds of the compound (I) are shown in the following.

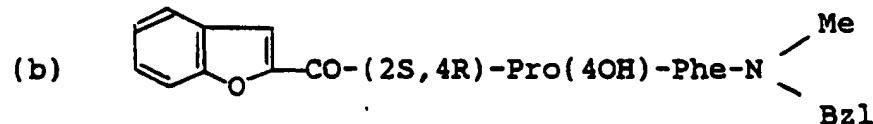
Test Compounds :

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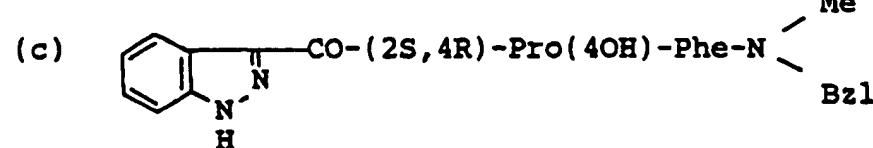


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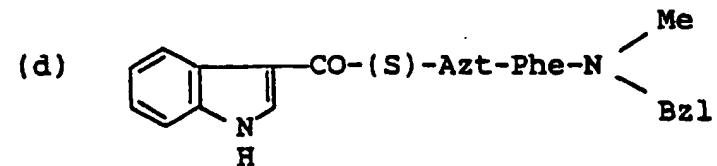


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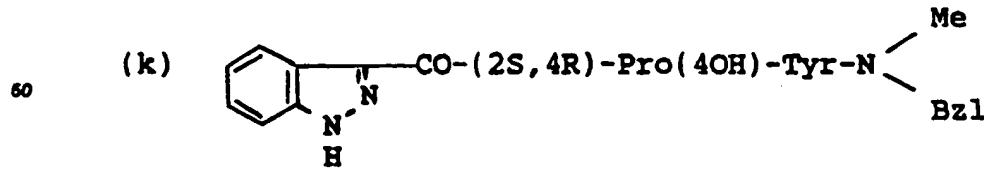
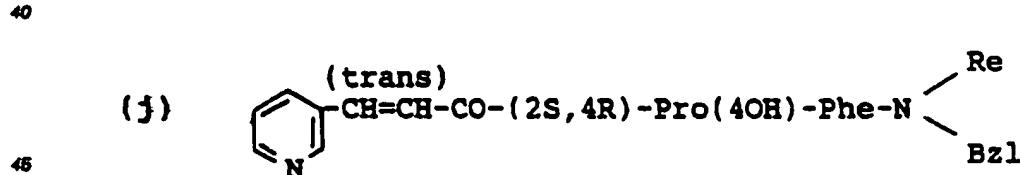
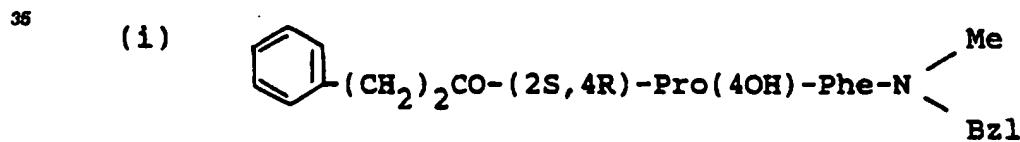
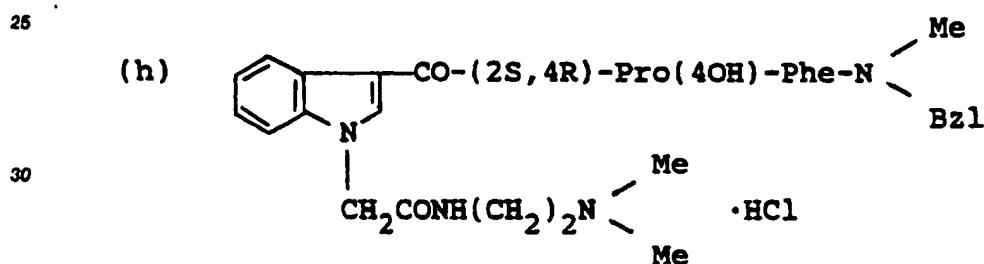
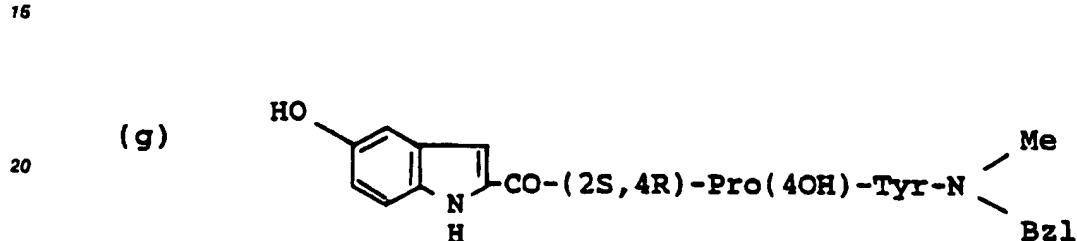
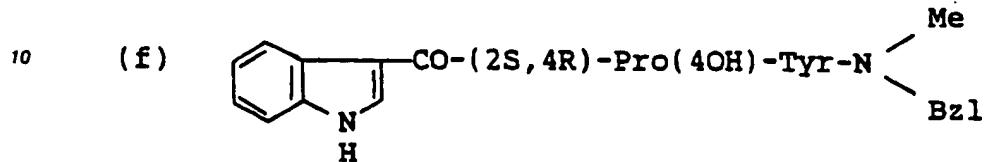
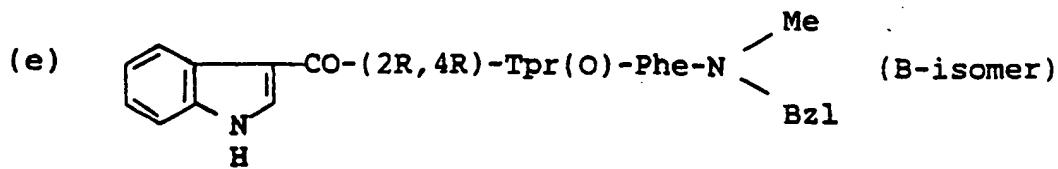
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(1) ³H-Substance P receptor binding

Test Method :

(a) Crude lung membrane preparation

5 Male Hartly strain guinea pigs were sacrificed by decapitation. The trachea and lung were removed and homogenized in buffer (0.25 M sucrose, 50 mM Tris-HCl pH 7.5, 0.1 mM EDTA) by using Polytoron (Kinematica). The homogenate was centrifuged (1000 xg, 10 min) to remove tissue clumps and the supernatant was centrifuged (14000 xg 20 min) to yield pellets. The pellets were resuspended in buffer (5 mM Tris-HCl pH 7.5), homogenized with a teflon homogenizer and centrifuged (14000 xg, 20 min) to yield pellets which were referred to as crude membrane fractions. The obtained pellets were stored at -70 °C until use.

15 (b) 3 H-Substance P binding to preparation membrane

16 Frozen crude membrane fractions were thawed and resuspended in Medium 1 (50 mM Tris-HCl pH 7.5, 5 mM MnCl₂, 0.02% BSA, 2 μ g/ml chymostatin, 4 μ g/ml leupeptin, 40 μ g/ml bacitracin.) 3 H-substance P (1 nM) was incubated with 100 μ l of the membrane preparation in Medium 1 at 4 °C for 30 minutes in a final 20 volume of 500 μ l. At the end of the incubation period, reaction mixture was quickly filtered over a Whatman GF/B glass filter (pretreated with 0.1% polyethylene imine for 3 hours prior to use) under aspiration. The filters were then washed four times with 5 ml of the buffer (50 mM Tris-HCl, pH 7.5). The radioactivity was counted in 5 ml of Aquazol-2 in Packard scintillation counter (Packard TRI -CARB 4530).

25

Test Results :		
	Test Compounds (0.1 μ l/ml)	Inhibition (%)
30	(a)	96
	(b)	99
	(c)	99
35	(d)	93
	(e)	100
	(f)	100
40	(g)	98
	(h)	100
	(i)	98
45	(j)	94
	(k)	100

50 (2) Effect of intratrachea administration on substance P induced bronchoconstriction in guinea-pigs.

Test Method :

55 Male Hartley strain guinea-pigs weighing 300-500 g were immobilized with sodium pentobarbital (10 mg/animal administered intraperitoneally). A catheter was also intubated into trachea for artifical ventilation. The animal was respirated by means of a miniature respiration pump (Harvard B-34, 5 ml/stroke, 60

strokes/minutes). Test Compound was suspended in 0.1% methyl cellulose-saline) and administered intratrachea.

Test Results :		
	Test Compounds	ED ₅₀ (mg/kg)
6	(a)	0.072
10	(k)	0.08

The following examples are given for purpose of illustrating the present invention in detail.

16 In these examples, there are employed the following abbreviations in addition to the abbreviations adopted by the IUPAC-IUB.

Ac : acetyl

Alb : 2-aminoisobutyric acid

Azt : azetidine-2-carboxylic acid

Boc : t-butoxycarbonyl

20 BSA : bistrimethylsilylacetamide

Bu^t : t-butyl

Bz : benzoyl

Bzl : benzyl

Bzl(o-F) : o-fluorobenzyl

25 Bzl(m-F) : m-fluorobenzyl

Bzl(o-CF₃) : o-trifluoromethylbenzyl

DMAP : dimethylaminopyridine

DMF : dimethylformamide

DMSO : dimethylsulfoxide

30 Et : ethyl

HOBT : N-hydroxybenzotriazole

IPE : isopropyl ether

Me : methyl

Ms : mesyl

35 NMM : N-methylmorpholine

4N-HCl/DOX : 4N-hydrogen chloride in 1,4-dioxane

Pr^t : isopropyl

Py(2) : 2-pyridyl

40 Su : succinimid

TEA : triethylamine

TFA : trifluoroacetic acid

THF : tetrahydrofuran

Tpr : thioproline

Ts : tosyl

45 WSC : 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide

Z : benzyloxycarbonyl

The Starting Compounds used and the Object Compounds obtained in the following examples are given in The Table as below, in which the formulae of the Starting Compounds are in the upper and the formulae of the Object Compounds are in the lower, respectively.

50

55

Table

Preparation No.	Formula
5	Boc-Phe-OH
	Boc-Phe-N Me Bzl
10	Boc-Phe-N Me Bzl
	HCl·H-Phe-N Me Bzl
15	HCl·H-Phe-N Me Bzl
	HCl·H-Phe-N Me Bzl
20	Boc-(2S,4R)-Pro(4OH)-Phe-N Me Bzl
	Boc-(2S,4R)-Pro(4OH)-Phe-N Me Bzl
25	HCl·H-(2S,4R)-Pro(4OH)-Phe-N Me Bzl
	HCl·H-(2S,4R)-Pro(4OH)-Phe-N Me Bzl
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35	

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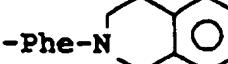
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Preparation No.	Formula
5	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{Boc-Pro-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
10	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{Boc-D-Pro-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
15	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{Boc-Gly-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
20	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{Boc-Ser-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
25	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{Boc-Asn-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
30	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{Boc-Aib-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
35	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{Boc-Asn-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
40	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{Boc-Asn-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
45	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{Boc-Aib-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
50	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{Boc-Aib-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$

Preparation No.	Formula
5	H-(2S,4S)-Pro(4OH)-OH
	Boc-(2S,4S)-Pro(4OH)-OH
10	H-(S)-Azt-OH
	Boc-(S)-Azt-OH
15	HCl·H-Phe-N^{Me} Bzl
	Boc-(2S,4S)-Pro(4OH)-Phe-N^{Me} Bzl
20	HCl·H-Phe-N^{Me} Bzl
	Boc-(2S)-Azt-Phe-N^{Me} Bzl
25	HCl·H-Phe-N^{Me} Bzl
	Boc-Tpr-Phe-N^{Me} Bzl
30	Boc-Tyr-OH
	Boc-Tyr-N^{Me} Bzl
35	Boc-Tyr-N^{Me} Bzl
	Boc-(2S,4R)-Pro(4OH)-Tyr-N^{Me} Bzl
40	
45	
50	

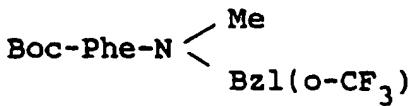
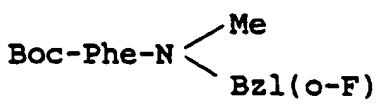
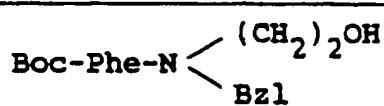
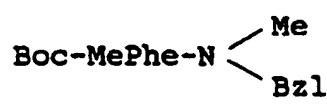
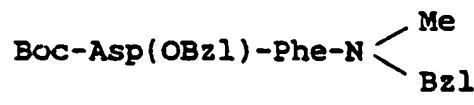
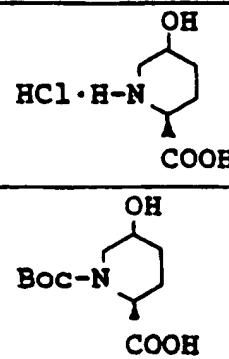
Preparation No.	Formula
6	
11	Boc-(2S,4R)-Pro(4OH)-Phe-N $\begin{array}{c} \text{Me} \\ \swarrow \\ \text{Bzl} \end{array}$
10	Boc-(2S,4R)-Pro(4OCONHCOCl ₃)-Phe-N $\begin{array}{c} \text{Me} \\ \swarrow \\ \text{Bzl} \end{array}$
15	
12	Boc-(2S,4R)-Pro(4OCONHCOCl ₃)-Phe-N $\begin{array}{c} \text{Me} \\ \swarrow \\ \text{Bzl} \end{array}$
20	
13	Boc-(2S,4R)-Pro(4OCONH ₂)-Phe-N $\begin{array}{c} \text{Me} \\ \swarrow \\ \text{Bzl} \end{array}$
25	HCl·H-(2S,4R)-Pro(4OCONH ₂)-Phe-N $\begin{array}{c} \text{Me} \\ \swarrow \\ \text{Bzl} \end{array}$
30	
14	Boc-(2S,4R)-Pro(4OH)-Phe-N $\begin{array}{c} \text{Me} \\ \swarrow \\ \text{Bzl} \end{array}$
35	
14	Boc-(2S,4R)-Pro(4OCH ₂ CO ₂ Et)-Phe-N $\begin{array}{c} \text{Me} \\ \swarrow \\ \text{Bzl} \end{array}$
40	
15	Boc-(2S,4R)-Pro(4OCH ₂ CO ₂ Et)-Phe-N $\begin{array}{c} \text{Me} \\ \swarrow \\ \text{Bzl} \end{array}$
45	
16	HCl·H-Phe-N $\begin{array}{c} \text{Me} \\ \swarrow \\ \text{Bzl} \end{array}$
50	
	Boc-Asp(OBzl)-Phe-N $\begin{array}{c} \text{Me} \\ \swarrow \\ \text{Bzl} \end{array}$

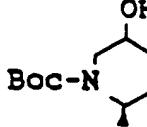
Preparation No.	Formula
5 17	$\text{HCl} \cdot \text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{Boc-Asp(OBzl)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
10 18	$\text{Boc-Asp(OBzl)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{HCl} \cdot \text{H-Asp(OBzl)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
20 19	Boc-Tyr-OH
25 19	$\text{Boc-Tyr-N} \begin{cases} \text{Me} \\ \text{CH}_2\text{Py(2)} \end{cases}$
30 20	Boc-Phe-N 
	Boc-Pro-Phe-N 
35 21-(1)	$\text{Boc-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl(o-F)} \end{cases}$
	$\text{HCl} \cdot \text{H-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl(o-F)} \end{cases}$
40 21-(2)	$\text{Boc-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl(o-CF}_3\text{)} \end{cases}$
	$\text{HCl} \cdot \text{H-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl(o-CF}_3\text{)} \end{cases}$

Preparation No.	Formula
6 21-(3)	Boc-(2S,4R)-Pro(4OH)-Phe-N Me Bzl(m-F)
	HCl·H-(2S,4R)-Pro(4OH)-Phe-N Me Bzl(m-F)
10 15 21-(4)	Boc-Pro-Phe-N Me Bzl
	HCl·H-Pro-Phe-N Me Bzl
20 25 30 35 40 45 50 55 60 21-(5)	Boc-Phe-N Me Bzl(o-F)
	HCl·H-Phe-N Me Bzl(o-F)
30 35 40 45 50 55 60 21-(6)	Boc-Phe-N Me Bzl(o-CF ₃)
	HCl·H-Phe-N Me Bzl(o-CF ₃)
40 45 50 55 60 21-(7)	Boc-Phe-N Me Bzl(m-F)
	HCl·H-Phe-N Me Bzl(m-F)
45 50 55 60 21-(8)	Boc-Ser-Phe-N Me Bzl
	HCl·H-Ser-Phe-N Me Bzl

Preparation No.	Formula
5	Boc-(2S,4R)-Pro(4OH)-Tyr-N^{Me} CH₂Py(2)
10	2HCl·H-(2S,4R)-Pro(4OH)-Tyr-N^{Me} CH₂Py(2)
15	Boc-(2S,4R)-Pro(4OH)-Phe-N^{Me} CH₂Py(2)
20	2HCl·H-(2S,4R)-Pro(4OH)-Phe-N^{Me} CH₂Py(2)
25	Boc-(2S,4R)-Pro(4OH)-Phe-N^{(CH₂)₂OAC} Bzl
30	HCl·H-(2S,4R)-Pro(4OH)-Phe-N^{(CH₂)₂OAC} Bzl
35	HCl·H-Phe-N^{Me} Bzl
40	Boc-Lys(Z)-Phe-N^{Me} Bzl
45	HCl·H-Phe-N^{Me} Bzl
50	Boc-Orn(Z)-Phe-N^{Me} Bzl

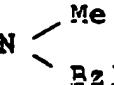
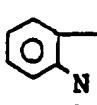
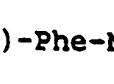
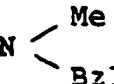
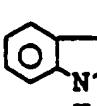
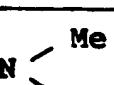
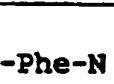
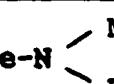
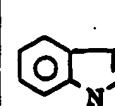
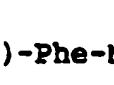
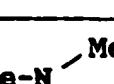
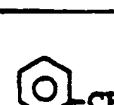
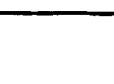
Preparation No.	Formula
6	$\text{Boc-Asp-Phe-N} \begin{cases} \text{Gln-NHBu}^t \\ \text{Me} \\ \text{Bzl} \end{cases}$
10	$\text{HCl \cdot H-Asp-Phe-N} \begin{cases} \text{Gln-NHBu}^t \\ \text{Me} \\ \text{Bzl} \end{cases}$
15	$\text{Boc-Lys(Cl-Z)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
20	$\text{HCl \cdot H-Lys(Cl-Z)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
25	$\text{Boc-Lys(Z)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
30	$\text{HCl \cdot H-Lys(Z)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
35	$\text{Boc-Orn(Z)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
40	$\text{HCl \cdot H-Orn(Z)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
45	$\text{Boc-MePhe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
50	$\text{HCl \cdot H-MePhe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
55	Boc-Phe-OH
60	$\text{Boc-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl(m-F)} \end{cases}$

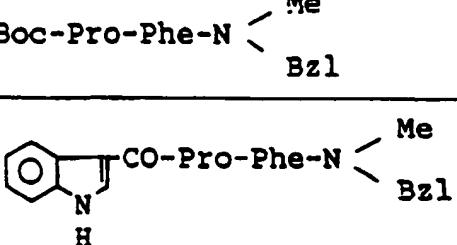
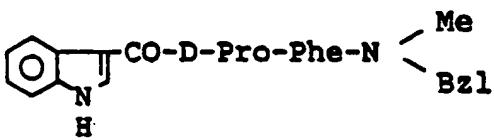
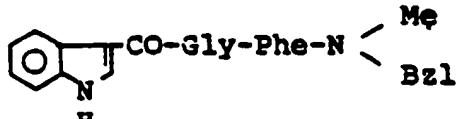
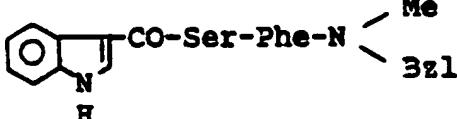
Preparation No.	Formula
5	Boc-Phe-OH
10	Boc-Phe-N 
15	Boc-Phe-OH
20	Boc-Phe-N 
25	Boc-Phe-OH
30	Boc-Phe-N 
35	Boc-MePhe-OH
40	Boc-MePhe-N 
45	Boc-Asp(OBzl)-Phe-N 
50	

Preparation No.	Formula
5 29-(1)	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	
10 29-(2)	$\text{Boc-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{HCl}\cdot\text{H-MePhe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
15 29-(3)	$\text{Boc-Pro-MePhe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl}(\text{o-CF}_3) \end{cases}$
20 29-(4)	$\text{Boc-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl}(\text{o-CF}_3) \end{cases}$
	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl(m-F)} \end{cases}$
25 29-(5)	$\text{Boc-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl(m-F)} \end{cases}$
	$\text{HCl}\cdot\text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl}(\text{o-F}) \end{cases}$
30 35 40 45	$\text{Boc-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl}(\text{o-F}) \end{cases}$

Preparation No.	Formula
6	$\text{HCl} \cdot \text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
10	$\text{Boc-(2S,4R)-Pro(4OMe)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
15	$\text{HCl} \cdot \text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
20	$\text{Boc-Ala-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
25	$\text{HCl} \cdot \text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
30	$\text{Boc-Thr-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
35	$\text{HCl} \cdot \text{H-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
40	$\text{Boc-Met-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
45	$\text{HCl} \cdot \text{H-MePhe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
50	$\text{Boc-Ser(Bzl)-MePhe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
55	$\text{HCl} \cdot \text{H-MePhe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
60	$\text{Z-Ser(Bu}^t\text{)-MePhe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$

Preparation No.	Formula
5 30-(1)	Boc-Tyr-N^{Me} CH₂Py(2)
	Boc-(2S,4R)-Pro(4OH)-Tyr-N^{Me} CH₂Py(2)
10 30-(2)	Boc-Phe-N^{Me} CH₂Py(2)
	Boc-(2S,4R)-Pro(4OH)-Phe-N^{Me} CH₂Py(2)
15 30-(3)	Boc-Phe-N^{(CH₂)OAc} Bzl
	Boc-(2S,4R)-Pro(4OH)-Phe-N^{(CH₂)OAc} Bzl
20 31	Boc-Asp-Phe-N^{Me} Bzl
	Boc-Asp-Phe-N^{Gln-NHBu^t} Bzl
25 32	Boc-Phe-N^{(CH₂)OH} Bzl
	Boc-Phe-N^{(CH₂)OAc} Bzl
30 33	Z-Ser(Bu^t)-MePhe-N^{Me} Bzl
	H-Ser(Bu^t)-MePhe-N^{Me} Bzl
35 34	Boc-(2S,4R)-Pro(4OH)-OH
	Boc-(2S,4R)-Pro(4OMe)-OH

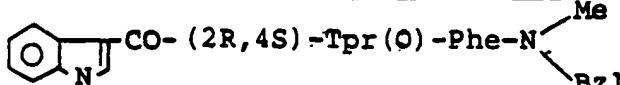
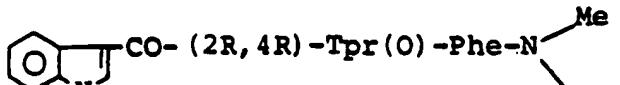
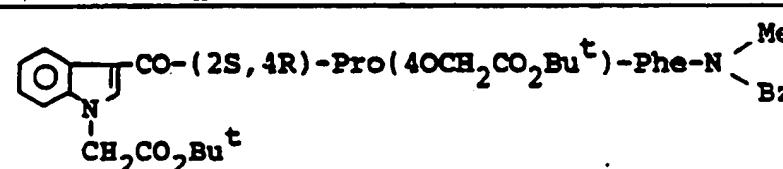
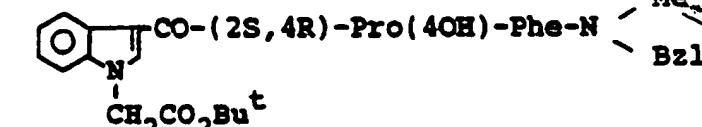
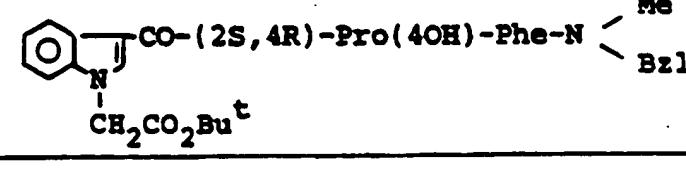
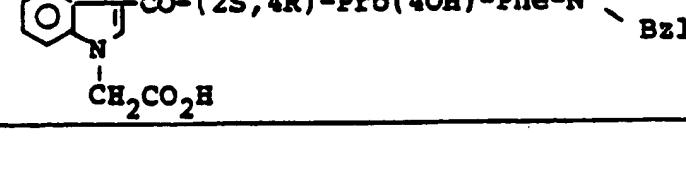
Example No.	Formula
5	<p>1</p> <p>Boc-(2S,4R)-Pro(4OH)-Phe-N </p>
10	<p>10</p> <p> CO-(2S,4R)-Pro(4OH)-Phe-N </p>
15	<p>15</p> <p>2</p> <p>Boc-(2S,4R)-Pro(4OH)-Phe-N </p>
20	<p>20</p> <p> CO-(2S,4R)-Pro(4OH)-Phe-N </p>
25	<p>25</p> <p>3</p> <p>Boc-(2S,4R)-Pro(4OH)-Phe-N </p> <p> (trans) CH=CHCO-(2S,4R)-Pro(4OH)-Phe-N </p>
30	<p>30</p> <p>4</p> <p>HCl·H-(2S,4R)-Pro(4OH)-Phe-N </p>
35	<p>35</p> <p> CH2CO-(2S,4R)-Pro(4OH)-Phe-N </p>
40	<p>40</p> <p>5</p> <p>HCl·H-(2S,4R)-Pro(4OH)-Phe-N </p>
45	<p>45</p> <p> CH2CO-(2S,4R)-Pro(4OH)-Phe-N </p>

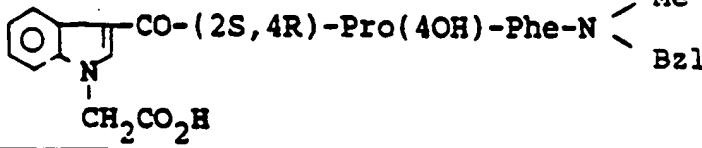
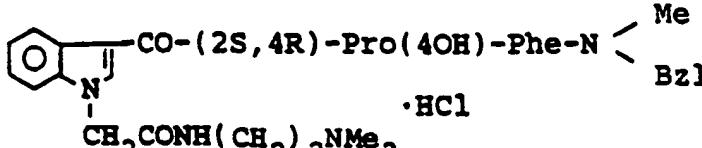
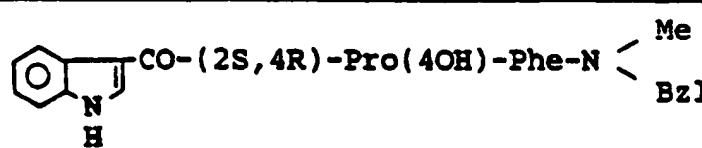
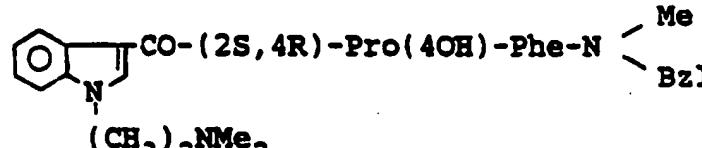
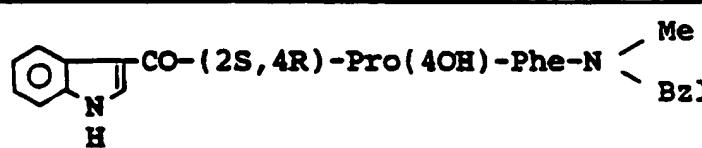
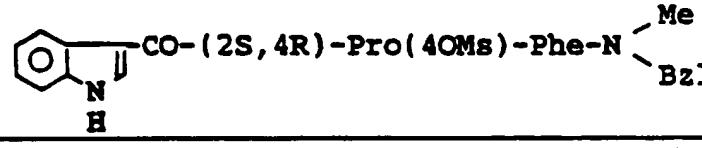
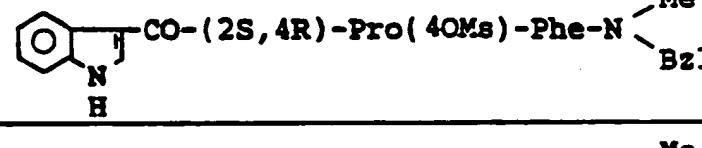
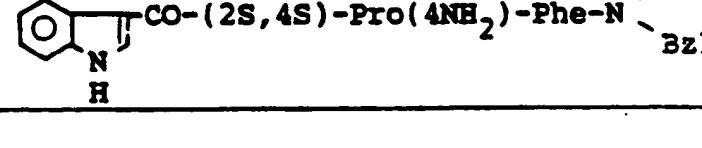
Example No.	Formula
5 6-(1)	Boc-Pro-Phe-N < Me Bzl
10 6-(1)	
15 6-(2)	Boc-D-Pro-Phe-N < Me Bzl
20 6-(2)	
25 6-(3)	Boc-Gly-Phe-N < Me Bzl
30 6-(3)	
35 6-(4)	Boc-Ser-Phe-N < Me Bzl
40 6-(4)	
45 6-(5)	Boc-Asn-Phe-N < Me Bzl
50 6-(5)	

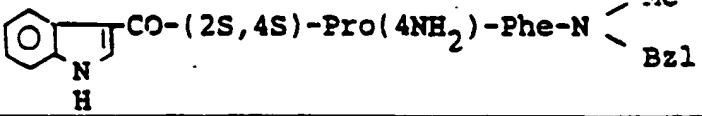
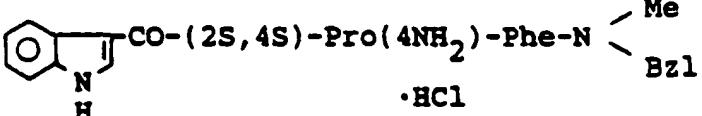
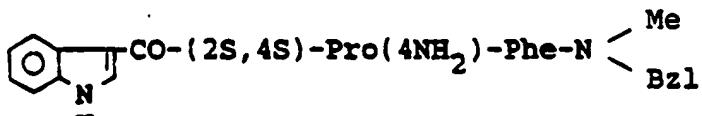
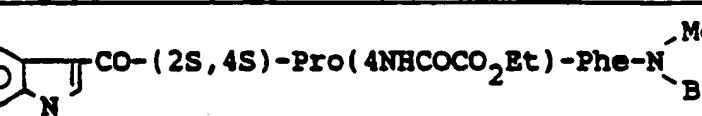
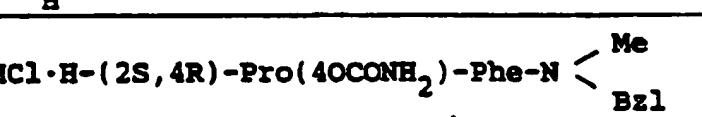
Example No.	Formula
5	
6-(6)	$\text{Boc-Aib-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
10	
15	$\text{CO-Aib-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
20	
16	$\text{Boc-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
25	
7-(1)	$\text{HO-CO-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
30	
7-(2)	$\text{Boc-Pro-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
35	
8	$\text{Boc-Pro-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
40	
9-(1)	$\text{HCl}\cdot\text{H-}(2S,4R)-\text{Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
45	
9-(2)	$\text{HCl}\cdot\text{H-}(2S,4R)-\text{Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
50	
60	$\text{HCl}\cdot\text{H-}(2S,4R)-\text{Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$

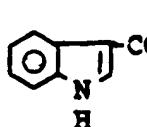
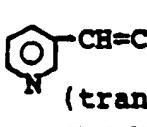
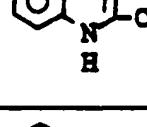
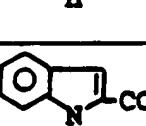
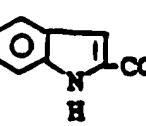
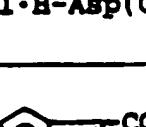
Example No.	Formula
5	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
10	$\text{O} \text{---} \text{NHCH}_2\text{CO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
15	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
20	$\text{HO} \text{---} \text{C}_6\text{H}_4 \text{---} \text{CH}_2\text{CO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
25	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
30	$\text{H} \text{---} \text{C}_6\text{H}_4 \text{---} \text{CO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
35	$\text{Boc}-(2S,4S)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
40	$\text{Boc}-(S)-\text{Azt}-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
45	$\text{Boc}-(S)-\text{Azt}-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
50	$\text{Boc}-\text{Tpr}-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
55	$\text{Boc}-\text{Tpr}-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$

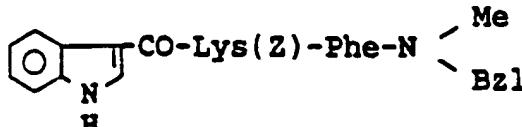
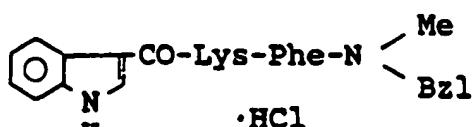
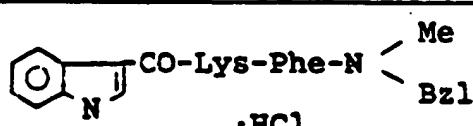
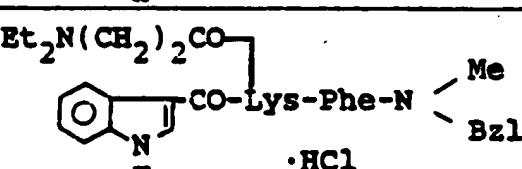
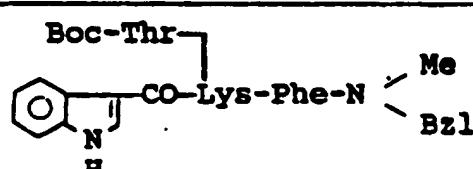
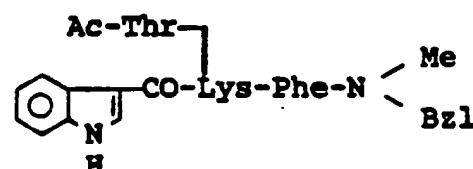
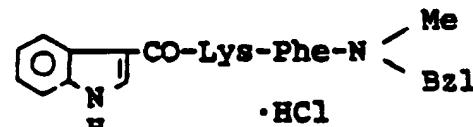
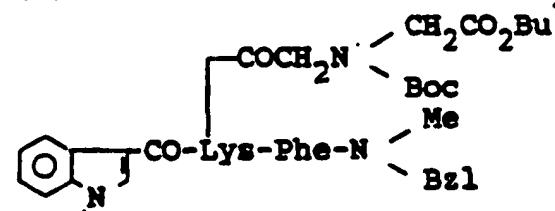
Example No.	Formula
5	
10-(4)	Boc-(2S,4R)-Pro(4OH)-Tyr-N ^{Me} Bzl
10	
15	
11-(1)	HCl·H-(2S,4R)-Pro(4OH)-Phe-N ^{Me} Bzl
20	
25	
11-(2)	HCl·H-(2S,4R)-Pro(4OH)-Phe-N ^{Me} Bzl
30	
35	
12-(1)	Boc-(2S,4R)-Pro(4OH)-Tyr-N ^{Me} Bzl
40	
45	
12-(2)	Boc-(2S,4R)-Pro(4OH)-Tyr-N ^{Me} Bzl
50	

Ex- ample No.	Formula
13	 <p>CO- (2R,4S)-Tpr(O)-Phe-N(Me)-Bzl</p>
14	 <p>CO- (2R,4R)-Tpr(O)-Phe-N(Me)-Bzl</p>
15	 <p>CO- (2S,4R)-Pro(4OH)-Phe-N(Me)-Bzl</p> <p>CH₂CO₂Bu^t</p>
15	 <p>CO- (2S,4R)-Pro(4OH)-Phe-N(Me)-Bzl</p> <p>CH₂CO₂H</p>
16	 <p>CO- (2S,4R)-Pro(4OH)-Phe-N(Me)-Bzl</p> <p>CH₂CO₂Bu^t</p>
16	 <p>CO- (2S,4R)-Pro(4OH)-Phe-N(Me)-Bzl</p> <p>CH₂CO₂H</p>

Example No.	Formula
5 17	 CO-(2S,4R)-Pro(4OH)-Phe-N(Me) Bzl CH ₂ CO ₂ H
10 18	 CO-(2S,4R)-Pro(4OH)-Phe-N(Me) Bzl CH ₂ CONH(CH ₂) ₂ NMe ₂ · HCl
15 19	 CO-(2S,4R)-Pro(4OH)-Phe-N(Me) Bzl CH ₂ CO ₂ H
20 20	 CO-(2S,4R)-Pro(4OH)-Phe-N(Me) Bzl (CH ₂) ₂ NMe ₂
25 19	 CO-(2S,4R)-Pro(4OH)-Phe-N(Me) Bzl CH ₂ CO ₂ H
30 35	 CO-(2S,4R)-Pro(4OMs)-Phe-N(Me) Bzl CH ₂ CO ₂ H
35 40	 CO-(2S,4R)-Pro(4OMs)-Phe-N(Me) Bzl CH ₂ CO ₂ H
40 45	 CO-(2S,4R)-Pro(4NH ₂)-Phe-N(Me) Bzl CH ₂ CO ₂ H

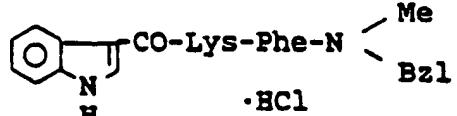
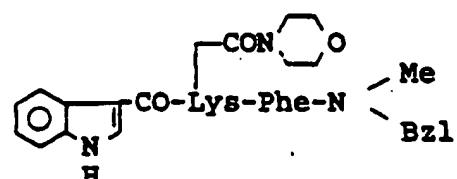
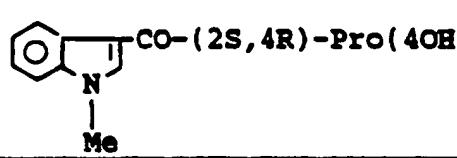
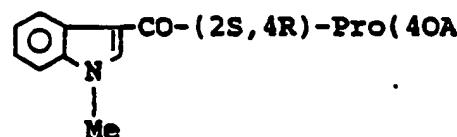
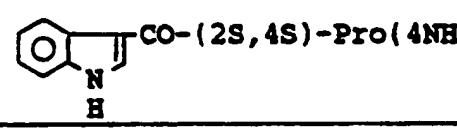
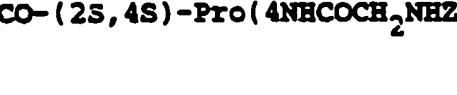
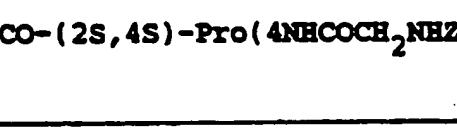
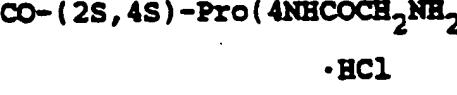
Example No.	Formula
5 21	
10 22	
15 23	
20 24	
25 25-(1)	
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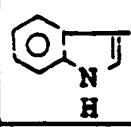
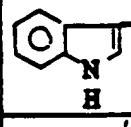
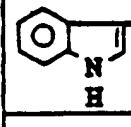
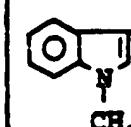
Example No.	Formula
6 25-(2)	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OCH}_2\text{CO}_2\text{Et})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
10 26	$\text{CO}-(2S,4R)-\text{Pro}(4\text{OCH}_2\text{CO}_2\text{Et})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$ 
15 27	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
20 28	$\text{CH}=\text{CHCO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$ (trans) $\cdot \text{HCl}$ 
25 29	$\text{CO-Asp(OBz1)-Phe-N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$ $\text{CO-Asp-Phe-N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$ $\text{CO-Asp-Phe-N} \begin{cases} \text{Gln-NHBu}^t \\ \text{Me} \end{cases} \begin{cases} \text{Bz1} \end{cases}$ $\text{HCl} \cdot \text{H-Asp(OBz1)-Phe-N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$ 
30 40	$\text{CO-Asp-Phe-N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$ 
35 45	$\text{CO-Asp-Phe-N} \begin{cases} \text{Gln-NHBu}^t \\ \text{Me} \end{cases} \begin{cases} \text{Bz1} \end{cases}$ $\text{HCl} \cdot \text{H-Asp(OBz1)-Phe-N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$ 
40 50	$\text{CO-Asp(OBz1)-Phe-N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$ 

Example No.	Formula
5 30	
10 31	
15 32	
20 33	
25 32	
30 36	
35 33	
40 45	

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Ex- ample No.	Formula
5 10 15 20 25 30 35 40 45	<p>34</p> 
	
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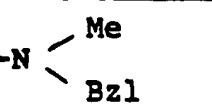
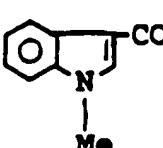
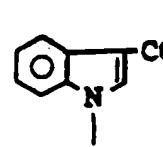
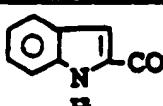
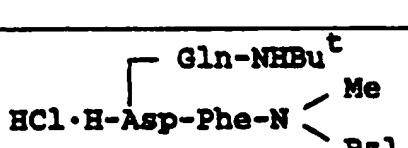
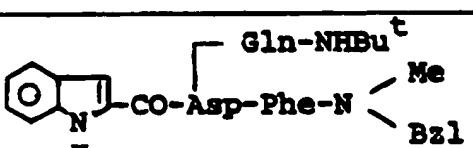
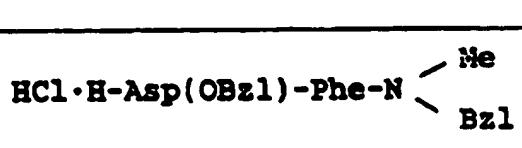
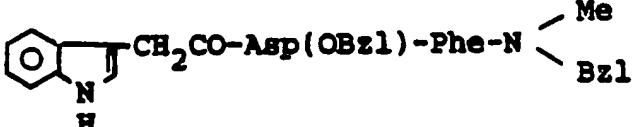
Ex- ample No.	Formula
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37	
38	 <p>(S) CO-(2S,4S)-Pro(4NHCO(CH₂)₂CHCO₂Bzl)-Phe-N(Me) Bzl</p>
39	 <p>(S) CO-(2S,4S)-Pro(4NHCO(CH₂)₂COONa)-Phe-N(Me) Bzl</p>
40	 <p>(S) CO-(2S,4S)-Pro(4NHCOOCO₂Et)-Phe-N(Me) Bzl</p>
41	 <p>(R) CO-(2S,4R)-Pro(4OH)-Phe-N(Me) Bzl</p>
42	 <p>(R) CO-(2S,4R)-Pro(4OH)-Phe-N(Me) Bzl</p>

Example No.	Formula
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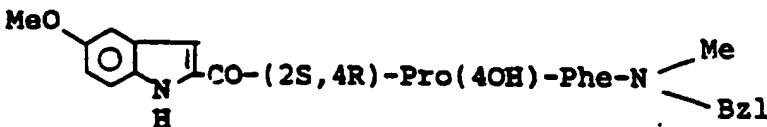
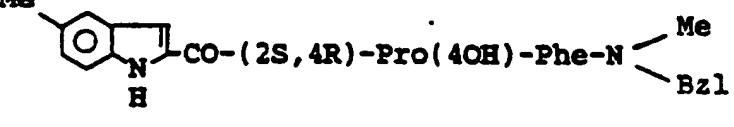
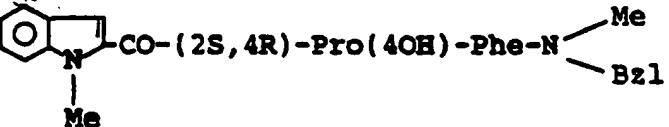
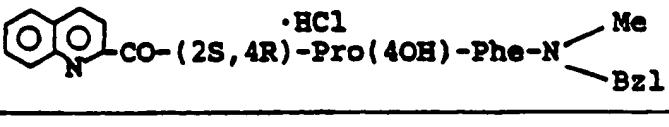
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Example No.	Formula
5 43-(4)	Boc-(2S,4R)-Pro(4OMe)-Phe-N  Bzl
10	
15 43-(5)	Boc-Ser(Bzl)-MePhe-N  Bzl
20	
25 44-(1)	HCl·H-Asp(OBzl)-Phe-N  Bzl
30	
35 44-(2)	HCl·H-Asp-Phe-N  Bzl
40	
45 44-(3)	HCl·H-Asp(OBzl)-Phe-N  Bzl
50	

Example No.	Formula
5	$\text{HCl} \cdot \text{H-Lys(Cl-Z)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
10	$\text{CO-Lys(Cl-Z)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
15	$\text{HCl} \cdot \text{H-Lys(Z)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
20	$\text{CH}_2\text{CO-Lys(Z)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
25	$\text{HCl} \cdot \text{H-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
30	$\text{CH}_2\text{CO-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
35	$\text{HO} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases} \text{-(CH}_2)_2\text{CO-(2S,4R)-Pro(4OH)-Phe-N}$
40	$\text{HCl} \cdot \text{H-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
45	$\text{CO-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$

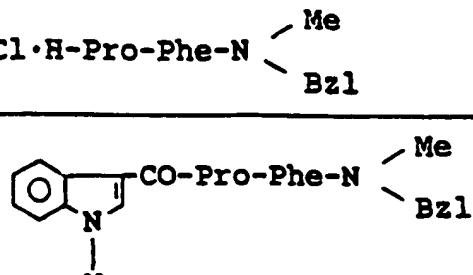
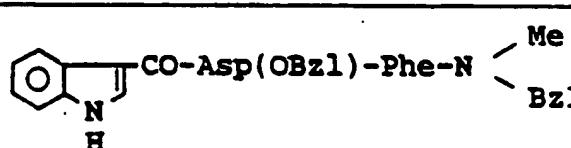
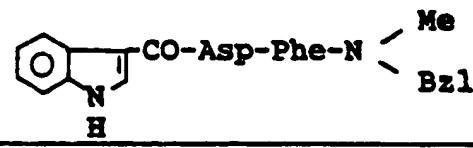
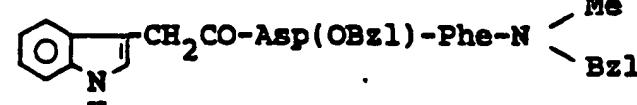
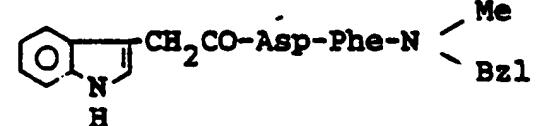
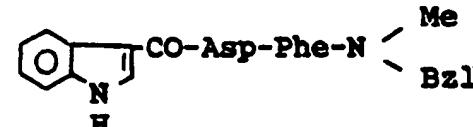
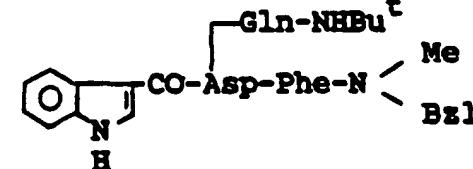
Example No.	Formula
5	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
10	$\text{CO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
15	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
20	$\text{CO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
25	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
30	$\text{Cl} \text{---} \text{CO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
35	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
40	$\text{HO} \text{---} \text{CH}=\text{CHCO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
45	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
50	$\text{HO} \text{---} \text{CH}=\text{CHCO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$

Example No.	Formula
8	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
10	$\text{Me}_2\text{CH}(\text{CH}_2)_2\text{CO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
15	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
20	
25	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
30	
35	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
40	
45	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
50	

Example No.	Formula
5 44-(19)	$\text{HCl}\cdot\text{H}-(2S,4R)\text{-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
10	
15 44-(20)	$\text{CH}_2\text{CO}-(2S,4R)\text{-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
20	
25 44-(21)	$\text{HCl}\cdot\text{H-Ser-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
30	
35 44-(22)	$\text{HCl}\cdot\text{H}-(2S,4R)\text{-Pro(4OH)-Tyr-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
40	
45 44-(23)	$\text{HCl}\cdot\text{H}-(2S,4R)\text{-Pro(4OH)-Tyr-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
50	$\text{Me}_2\text{CH}(\text{CH}_2)_2\text{CO}-(2S,4R)\text{-Pro(4OH)-Tyr-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$

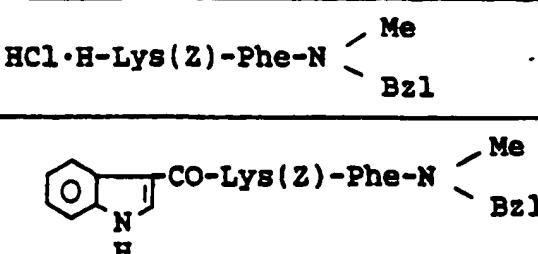
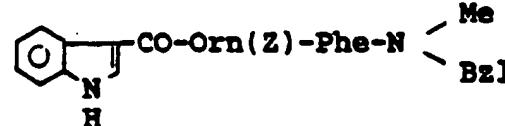
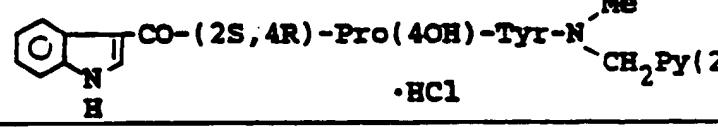
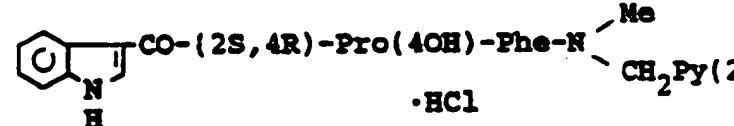
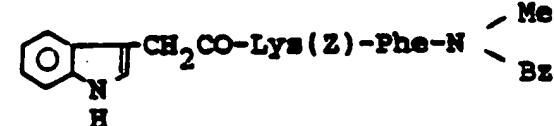
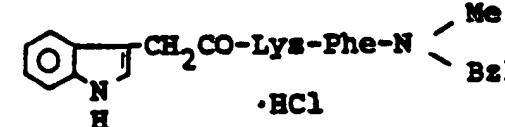
Example No.	Formula
5 44-(24)	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Tyr}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
10 44-(25)	$\text{CO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Tyr}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
15 44-(26)	$2\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Tyr}-\text{N} \begin{cases} \text{Me} \\ \text{CH}_2\text{Py}(2) \end{cases}$
20 44-(27)	$2\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{CH}_2\text{Py}(2) \end{cases}$
25 44-(28)	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} (\text{CH}_2)_2\text{OAc} \\ \text{Bz1} \end{cases}$
30 44-(29)	$\text{CO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} (\text{CH}_2)_2\text{OAc} \\ \text{Bz1} \end{cases}$
35 44-(30)	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
40 44-(31)	$\text{CO}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$

Example No.	Formula
5 44-(29)	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
10 44-(30)	$\text{HO} \begin{cases} \text{(trans)} \\ \text{CH=CHCO-} \end{cases} (2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1} \end{cases}$
15 44-(31)	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1(o-F)} \end{cases}$
20 44-(32)	$\text{CO-} \begin{cases} \text{(trans)} \\ \text{CH=CHCO-} \end{cases} (2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1(o-F)} \end{cases}$
25 44-(33)	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1(o-CF}_3 \text{)} \end{cases}$
30 44-(34)	$\text{CO-} \begin{cases} \text{(trans)} \\ \text{CH=CHCO-} \end{cases} (2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1(o-CF}_3 \text{)} \end{cases}$
35 44-(35)	$\text{HCl} \cdot \text{H}-(2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1(m-F)} \end{cases}$
40 44-(36)	$\text{CO-} \begin{cases} \text{(trans)} \\ \text{CH=CHCO-} \end{cases} (2S,4R)-\text{Pro}(4\text{OH})-\text{Phe}-\text{N} \begin{cases} \text{Me} \\ \text{Bz1(m-F)} \end{cases}$

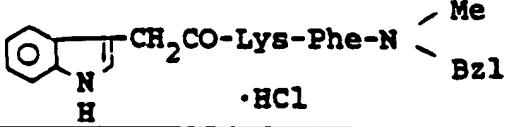
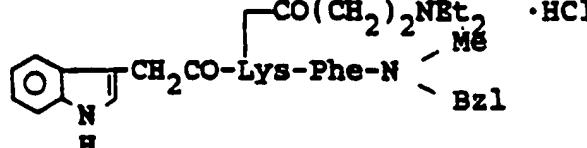
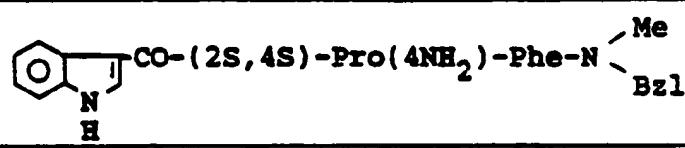
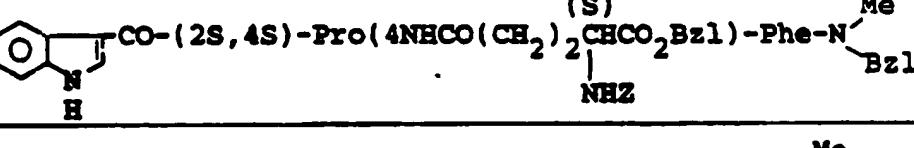
Example No.	Formula
5	$\text{HCl} \cdot \text{H-Pro-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$
10	$\text{CO-Pro-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$ 
15	$\text{CO-Asp(OBzl)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$ 
20	$\text{CO-Asp-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$ 
25	$\text{CH}_2\text{CO-Asp(OBzl)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$ 
30	$\text{CH}_2\text{CO-Asp-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$ 
35	$\text{CO-Asp-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$ 
40	$\text{Gln-NHBu}^t \text{ CO-Asp-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$ 

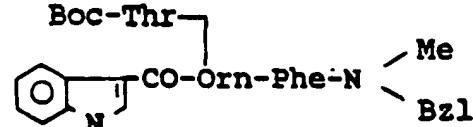
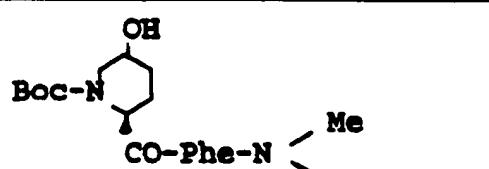
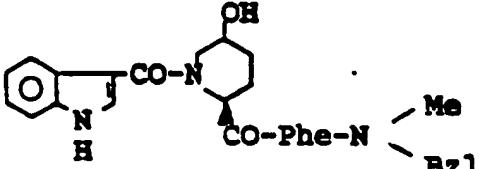
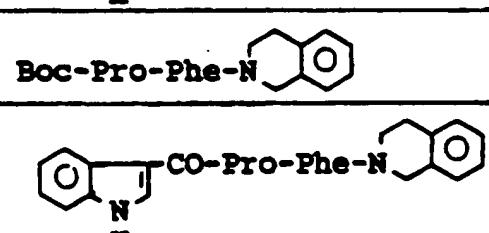
Example No.	Formula
46-(2)	<p>CO-Asp-Phe-N</p> <p>Me</p> <p>Bzl</p>
46-(3)	<p>CO-Asp-Phe-N</p> <p>Me</p> <p>Bzl</p>
46-(4)	<p>CO-Asp-Phe-N</p> <p>Me</p> <p>Bzl</p>
46-(5)	<p>CO-Asp-Phe-N</p> <p>Me</p> <p>Bzl</p>

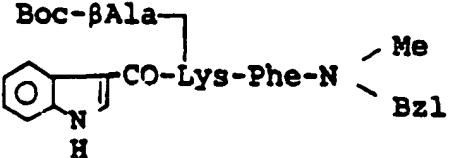
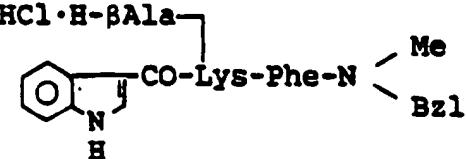
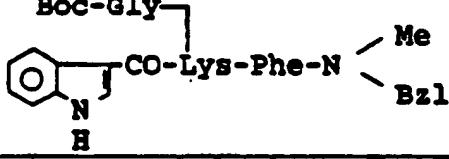
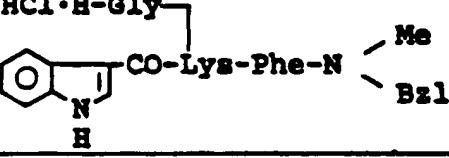
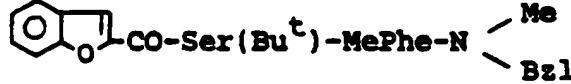
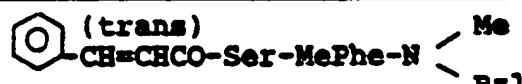
Example No.	Formula
46-(6)	
47-(1)	
47-(2)	
47-(3)	
47-(4)	
47-(5)	

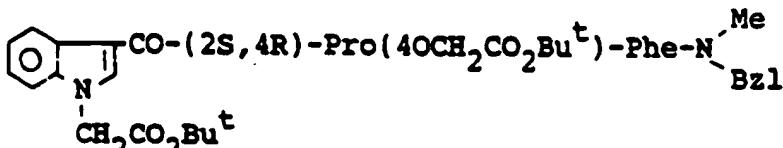
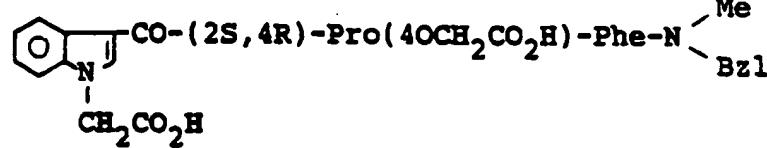
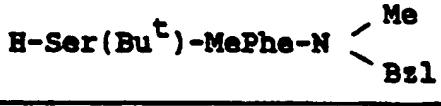
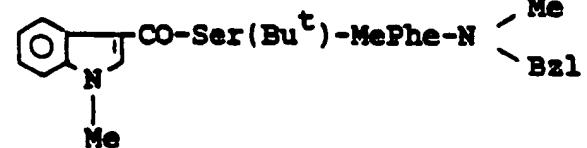
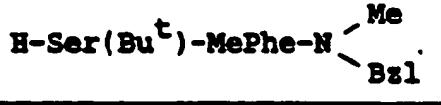
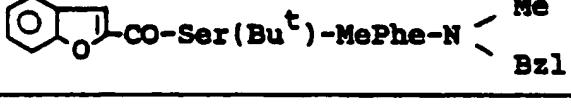
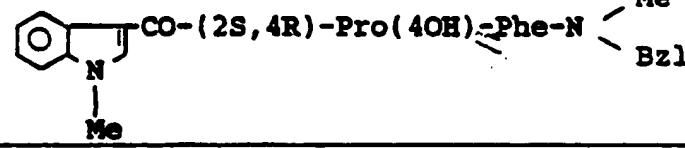
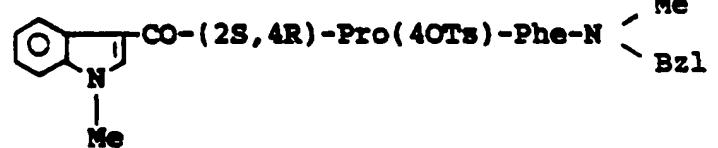
Example No.	Formula
48-(1)	$\text{HCl} \cdot \text{H-Lys(Z)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$ 
48-(2)	$\text{HCl} \cdot \text{H-Orn(Z)-Phe-N} \begin{cases} \text{Me} \\ \text{Bzl} \end{cases}$ 
48-(3)	$2\text{HCl} \cdot \text{H-(2S,4R)-Pro(4OH)-Tyr-N} \begin{cases} \text{Me} \\ \text{CH}_2\text{Py(2)} \end{cases}$ 
48-(4)	$2\text{HCl} \cdot \text{H-(2S,4R)-Pro(4OH)-Phe-N} \begin{cases} \text{Me} \\ \text{CH}_2\text{Py(2)} \end{cases}$ 
49-(1)	 

Example No.	Formula
5 49-(2)	 CO-Orn(Z)-Phe-NH ₂ Me Bzl
10	 CO-Orn-Phe-NH ₂ ·HCl Me Bzl
15 50-(1)	 CO-Lys-Phe-NH ₂ ·HCl Me Bzl
20	 Boc-Thr-CO-Lys-Phe-NH ₂ ·HCl Me Bzl
25 50-(2)	 CO-Lys-Phe-NH ₂ ·HCl Me Bzl
30	 Boc-βAla-CO-Lys-Phe-NH ₂ ·HCl Me Bzl
35 50-(3)	 CO-Lys-Phe-NH ₂ ·HCl Me Bzl
40	 Boc-Gly-CO-Lys-Phe-NH ₂ ·HCl Me Bzl
45	

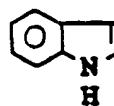
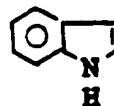
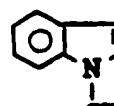
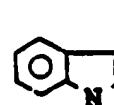
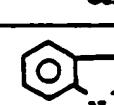
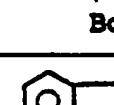
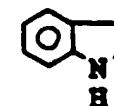
Ex- ample No.	Formula
50-(4)	 <p>•HCl</p>
50-(5)	 <p>•HCl</p>
50-(6)	 <p>•HCl</p>
50-(7)	 <p>•HCl</p>

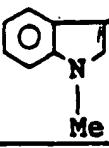
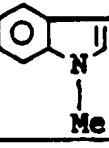
Example No.	Formula
5 10 15 20 25 30 35 40 45 50	<p>51-(1)</p>  <p>51-(2)</p>  <p>51-(3)</p>  <p>51-(4)</p> 

Example No.	Formula
5 52-(1)	<p>Boc-βAla-</p> 
10 52-(2)	<p>HCl·H-βAla-</p> 
15 53-(1)	<p>Boc-Gly-</p> 
20 53-(2)	<p>HCl·H-Gly-</p> 
25 53-(1)	
30 53-(2)	
35 53-(1)	
40 53-(2)	

Example No.	Formula
5 53-(3)	 <p>CO-(2S,4R)-Pro(4OCH₂CO₂Bu^t)-Phe-N(Me) Bzl</p>
10 54-(1)	 <p>CO-(2S,4R)-Pro(4OCH₂CO₂H)-Phe-N(Me) Bzl</p>
15 54-(1)	 <p>H-Ser(Bu^t)-MePhe-N(Me) Bzl</p>
20 54-(2)	 <p>CO-Ser(Bu^t)-MePhe-N(Me) Bzl</p>
25 54-(2)	 <p>H-Ser(Bu^t)-MePhe-N(Me) Bzl</p>
30 55	 <p>CO-Ser(Bu^t)-MePhe-N(Me) Bzl</p>
35 55	 <p>CO-(2S,4R)-Pro(4OH)-Phe-N(Me) Bzl</p>
40 55	 <p>CO-(2S,4R)-Pro(4OTs)-Phe-N(Me) Bzl</p>

Ex- ample No.	Formula
56-(1)	<p>(s) CO-(2S,4S)-Pro(4NHCOCH(CH₂)₂CO₂Bz1)-Phe-N<sup>Me</sup> <sub>NH</sub> Bz1</p>
56-(2)	<p>CO-(2S,4S)-Pro(4NHCOCH(CH₂)₂CO₂H)-Phe-N<sup>Me</sup> <sub>NH</sub> Bz1</p>
56-(2)	<p>CO-Ser(Bz1)-MePhe-N<sup>Me</sup> <sub>Me</sub> Bz1</p>
57	<p>CO-(2S,4S)-Pro(4NH₂)-Phe-N<sup>Me</sup> <sub>H</sub> Bz1</p>
58	<p>CO-(2S,4S)-Pro(4NHMs)-Phe-N<sup>Me</sup> <sub>H</sub> Bz1</p>
58	<p>CO-(2S,4S)-Pro(4NH₂)-Phe-N<sup>Me</sup> <sub>H</sub> Bz1</p>
58	<p>CO-(2S,4S)-Pro(4NHCO(CH₂)₂NH₂)-Phe-N<sup>Me</sup> <sub>H</sub> Bz1 •HCl</p>

Example No.	Formula
5 59	
10 60	
15 60	
20 61	
25 61	
30 62	
35 62	
40 62	
45 62	

Example No.	Formula
6	
10	

15

Preparation 1

20

A solution of Starting Compound (5.48 g) and NMM (2.09 g) in methylene chloride (50 ml) was cooled at -20 °C. To this solution was added dropwise isobutyl chloroformate (2.82 g) maintaining the temperature between -22 °C to -20 °C in 7 minutes. After stirring the mixture for 20 minutes at the same temperature, the solution was cooled to -35 °C and HNMeBzI (2.50 g) was added dropwise to the solution. The reaction mixture was stirred for 2 hours during which period the temperature was gradually raised to -2 °C. The solution was washed successively with water (twice), diluted sodium hydrogencarbonate solution (twice), water, 0.5N hydrochloric acid (twice) and sodium chloride solution, and dried over magnesium sulfate. After evaporation, the solidified residue was pulverized in hot IPE (10 ml), and after cooling, n-hexane (30 ml) was added to the mixture. The crystalline solid was filtered, washed with n-hexane (5 ml x 2), and dried to give Object Compound (8.49 g).

30

mp : 90-91.5 °C

IR (Nujol) : 3380, 1690, 1645 (sh), 1635, 1525 cm⁻¹NMR (CDCl₃, δ) : 1.37 (s) and 1.43 (s)(9H), 2.87 (s) and 2.87 (s)(3H), 3.04 (2H, d, J=7Hz), 4.28 (ABq, J=14Hz) and 4.52 (s)(2H); 4.80 (1H, m), 5.4 (1H, m), 7.0-7.4 (10H)

35

Elemental Analysis. Calculated for C ₂₃ H ₂₈ N ₂ O ₃ :

Found :	C 71.71, H 7.68, N 7.60
	C 72.04, H 7.85, N 7.85

40

[α]_D²⁵ + 19.99 ° (C = 1.035, CHCl₃)

45

Preparation 2

50

To an ice-cooled solution of Starting Compound (3.0 g) and anisole (3 ml) in methylene chloride (10 ml) was added TFA (12 ml). The solution was stirred for 15 minutes at this temperature and for additional half an hour at room temperature. After evaporation, addition and re-evaporation of 4N-HCl/DOX were repeated twice (4.1 ml and 2.0 ml, respectively). The residue was dissolved in ether (15 ml), and crystallized by seeding. After standing overnight, the crystals were filtered, washed with ether, and dried to give Object Compound (2.12 g).

mp : 133-135 °C

55

IR (Nujol) : 3400, 1650 cm⁻¹NMR (CDCl₃, δ) : 2.43 (s) and 2.70 (s)(3H), 3.5 (2H, m), 4.13 and 4.75 (2H, ABq, J=14Hz), 5.0 (1H, m), 7.0-7.4 (10H, m), 8.86 (3H, br s)

5

Elemental Analysis. Calculated for C ₁₇ H ₂₀ N ₂ O ⁺ HCl ⁻ 1/2H ₂ O :	
Found :	C 65.06, H 7.07, N 8.93
	C 65.53, H 6.86, N 8.90

[α]_D²⁵ + 57.78° (C = 1.066, CHCl₃)

10

Preparation 3

15 To an ice-cooled solution of Boc-(2S,4R)-Pro(4OH)-OH (1.80 g), Starting Compound (2.37 g), and HOBT (1.05 g) in methylene chloride (50 ml), was added WSC (1.21 g). The solution was stirred at the same temperature for two hours and at room temperature for two hours. After concentration, the product was extracted with ethyl acetate and the organic layer was washed successively with water, diluted sodium hydrogencarbonate solution, 0.5N hydrochloric acid and sodium chloride solution, and dried over anhydrous magnesium sulfate to give Object Compound (3.82 g) as an amorphous solid.
20 NMR (DMSO-d₆, δ) : 1.25 and 1.47 (9H, s), 1.5-2.1 (2H, m), 2.78 and 2.85 (3H, s), 2.8-3.1 (2H, m), 3.2-3.5 (3H, m), 4.1-4.25 (2H, m), 4.35-4.6 (2H, m), 4.8-5.1 (2H, m), 7.0-7.35 (10H, m), 8.3-8.4 (1H, m)

Preparation 4

25 Starting Compound (3.0 g) was dissolved in methylene chloride (30 ml), and to the solution 4N-HCl/DOX (30 ml) was added under ice-cooling and the solution was stirred at the same temperature for 10 minutes and further at room temperature for 40 minutes. After evaporation, the residue was triturated with IPE, filtered, washed with the same solvent, and dried under vacuum to give Object Compound (2.90 g).
30 NMR (DMSO-d₆, δ) : 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.75 (s) and 2.85 (s)(3H), 2.8-3.2 (3H, m), 3.2-3.4 (1H, m), 4.2-4.7 (4H, m), 4.85-5.05 (1H, m), 7.0-7.4 (10H, m), 8.59 (1H, broad), 9.24 (1H, d, J = 8Hz), 10.29 (1H, broad)

Preparation 5

35 The object compounds were obtained according to a similar manner to that of Preparation 3.
(1) IR (CH₂Cl₂) : 3400, 1700, 1650, 1505, 1385, 1170 cm⁻¹
NMR (CDCl₃, δ) : 1.47 (9H, s), 1.7-2.2 (4H, m), 2.87 and 2.87 (3H, s), 2.82-3.1 (2H, m), 3.27-3.52 (2H, m), 4.3 (1H, m), 4.40 and 4.82 (2H, ABq, J = 14Hz), 5.20 (1H, dt, J = 8Hz and 6Hz), 6.85-7.4 (10H, m)
40 (2) IR (CH₂Cl₂) : 3450, 1700, 1650 cm⁻¹
NMR (CDCl₃, δ) : 1.48 (9H, s), 1.8-1.9 (2H, m), 1.95-2.1 (2H, m), 2.58 and 2.81 (3H, s), 3.01 and 3.02 (2H, d, J = 7.2Hz), 3.5 (2H, m), 4.2-4.3 (1H, m), 4.38 and 4.58 (2H, ABq, J = 14.5Hz), 5.18 (1H, d, J = 7Hz), 6.7-7.0 (1H, m), 7.0-7.35 (10H, m)
(3) IR (Neat) : 3300, 1710, 1635, 1495 cm⁻¹
45 NMR (DMSO-d₆, δ) : 1.37 (9H, s), 2.73 (s) and 2.79 (s)(3H), 2.75-3.15 (2H, m), 3.35-3.70 (2H, m), 4.20-4.70 (2H, m), 4.75-5.20 (1H, m), 6.70-7.45 (11H, m), 8.00-8.35 (1H, m)
(4) IR (Neat) : 3300, 1710, 1640, 1630, 1480 cm⁻¹
NMR (DMSO-d₆, δ) : 1.37 (9H, s), 2.71 (s) and 2.77 (s)(3H), 2.7-3.2 (2H, m), 3.3-3.8 (2H, m), 3.8-4.1 (1H, m), 4.43 (2H, s), 4.73 (1H, t, J = 8Hz), 4.8-5.2 (1H, m), 6.4-6.8 (1H, m), 6.8-7.4 (10H, m), 8.0-8.2 (1H, m)
50 (5) IR (Nujol) : 3400, 3350, 3300, 3200, 1690, 1650, 1525 cm⁻¹
NMR (DMSO-d₆, δ) : 1.38 (9H, s), 2.20-2.45 (2H, m), 2.70 (s) and 2.75 (s)(3H), 2.75-3.15 (2H, m), 4.00-4.60 (3H, m), 4.75-5.10 (1H, m), 6.83 (2H, broad s), 6.90-7.50 (11H, m), 7.90-8.20 (1H, m)
(6) IR (Neat) : 3320, 1720, 1705, 1690, 1650, 1640, 1630 cm⁻¹
55 NMR (DMSO-d₆, δ) : 1.20 (s), 1.28 (s) and 1.29 (s)(6H), 1.38 (9H, s), 2.6-3.2 (2H, m), 2.72 (s) and 2.78 (s)(3H), 4.2-4.7 (2H, m), 4.8-5.2 (1H, m), 6.8-6.9 (1H, m), 7.0-7.4 (10H, m), 7.4-7.7 (1H, m)

Preparation 6

In a mixture of water (10 ml) and dioxane (5 ml), Starting Compound (1.0 g) was suspended. To the mixture TEA (1.06 ml) and di-tert-butyl dicarbonate (1.83 g) was added successively under ice-cooling. The mixture was stirred overnight at room temperature, then water (20 ml) was added. After washing with ethyl acetate (20 ml), the aqueous layer was cooled with ice bath and acidified with 5N-hydrochloric acid. The product was extracted with ethyl acetate, and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated. The residue was crystallized with a mixture of ethyl acetate and IPE, filtered and dried to give Object Compound (1.34 g).

5 mp : 145-146 °C

IR (Nujol) : 3450, 1735, 1675 cm⁻¹

10 NMR (DMSO-d₆, δ) : 1.34 (s) and 1.39 (s)(9H), 1.75-1.90 (1H, m), 2.20-2.40 (1H, m), 3.05-3.15 (1H, m), 3.40-3.55 (1H, m), 4.00-4.25 (2H, m)

Preparation 7

16

The object compound was obtained according to a similar manner to that of Preparation 6.

IR (Nujol) : 1780, 1640 cm⁻¹

17 NMR (DMSO-d₆, δ) : 1.48 (9H, s), 1.95-2.10 (1H, m), 2.40-2.60 (1H, m), 3.70-3.90 (2H, m), 4.44 (1H, dd, J=5 and 8Hz), 12.75 (1H, br s)

20

Preparation 8

The object compounds were obtained according to a similar manner to that of Preparation 3.

25

(1) IR (Neat) : 3300, 1680, 1635 cm⁻¹

NMR (DMSO-d₆, δ) : 1.28 (s), 1.39 (s) and 1.40 (s)(9H), 1.5-1.8 (1H, m), 2.2-2.4 (1H, m), 2.7-3.1 (5H, m), 3.1-3.3 (1H, m), 3.4-3.5 (1H, m), 4.1-4.2 (2H, m), 4.3-4.6 (2H, m), 4.9-5.1 (1H, m), 5.18 (1H, d, J=6Hz), 7.0-7.1 (2H, m), 7.1-7.3 (8H, m), 8.3-8.4 (1H, m)

(2) IR (Neat) : 1710, 1680, 1645 cm⁻¹

30

NMR (DMSO-d₆, δ) : 1.31 (9H, s), 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.78 (s) and 2.88 (s)(3H), 2.8-3.1 (2H, m), 3.7-3.9 (2H, m), 4.4-4.6 (3H, m), 4.9-5.1 (1H, m), 7.0-7.4 (10H, m), 8.25-8.35 (1H, m)

(3) IR (Neat) : 3300, 1705, 1640, 1485 cm⁻¹

NMR (DMSO-d₆, δ) : 1.31 (9H, s), 2.7-3.1 (8H, m), 3.2-3.4 (1H, m), 4.3-4.7 (5H, m), 4.9-5.1 (1H, m), 7.0-7.1 (3H, m), 7.1-7.3 (7H, m), 8.43 (1H, br t, J=8Hz)

35

Preparation 9

The object compound was obtained according to a similar manner to that of Preparation 1.

40 mp : 111-113 °C

IR (Neat) : 3300, 1680, 1640, 1525, 1415, 1285, 1170 cm⁻¹

NMR (DMSO-d₆, δ) : 1.25 (s), 1.29 (s) and 1.38 (s)(9H), 2.80-2.90 (2H, m), 2.73 (s) and 2.83 (s)(3H), 4.20-4.70 (3H, m), 6.80 (d, J=8Hz) and 6.85 (d, J=8Hz)(2H), 8.89 (d, J=8Hz) and 7.06 (d, J=8Hz)(2H), 7.10-7.40 (5H, m), 9.22 (1H, s)

45

Elemental Analysis. Calculated for C ₂₂ H ₂₃ N ₂ O ₆ :	
Found :	C 68.73, H 7.34, N 7.29 C 68.54, H 7.35, N 7.14

55

Preparation 10

The object compound was obtained according to similar manners to those of Preparation 2 and Preparation 3, successively.

IR (Nujol) : 3280, 1665, 1630, 1515 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.28 (s) and 1.39 (s)(3H), 1.60-1.90 (1H, m), 1.90-2.10 (1H, m), 2.60-3.00 (2H, m), 2.75 (s) and 2.82 (s)(3H), 3.20-3.30 (1H, m), 3.35-3.50 (1H, m), 4.10-4.70 (4H, m), 4.70-5.05 (2H, m), 6.60 (d, J = 8Hz) and 6.84 (d, J = 8Hz)(2H), 6.86 (d, J = 8Hz) and 7.03 (d, J = 8Hz)(2H), 6.90-7.10 (2H, m), 7.20-7.35 (3H, m), 8.20-8.40 (1H, m), 9.19 (s) and 9.23 (s)(1H)

Preparation 11

10 To a solution of Starting Compound (2.56 g) in methylene chloride (40 ml) was added trichloroacetyl isocyanate (1.0 g) under ice-cooling. After stirring for five minutes, the solution was washed with water, aqueous sodium hydrogencarbonate solution, and aqueous sodium chloride solution and dried over magnesium sulfate to give Object Compound (3.55 g).

IR (CH_2Cl_2) : 3400, 1810, 1740, 1690, 1645, 1480, 1160 cm^{-1}

15 NMR (CDCl_3 , δ) : 1.47 (9H, s), 2.1-2.4 (2H, m), 2.65 and 2.87 (3H, s), 2.85-3.1 (2H, m), 3.5-4.0 (2H, m), 4.3-4.83 (3H, m), 5.1-5.4 (2H, m), 7.0-7.4 (11H, m), 8.63 (1H, s)

Preparation 12

20 To a solution of Starting Compound (3.10 g) in methanol (50 ml) was added 1N-sodium hydroxide solution (4.8 ml). The solution was stirred for two hours at room temperature. After concentration, the product was extracted with ethyl acetate and the organic layer was washed with water, sodium chloride solution and dried over magnesium sulfate, to give Object Compound (2.75 g).

25 IR (CH_2Cl_2) : 3540, 3520, 1730, 1680, 1640, 1580 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.25 and 1.39 (9H, s), 1.75-2.0 and 2.1-2.3 (2H, m), 2.78 and 2.85 (3H, s), 2.8-3.1 (2H, m), 3.35-3.7 (2H, m), 4.2 (1H, m), 4.35-4.8 (2H, m), 4.9-5.05 (2H, m), 6.32 (2H, br s), 7.0-7.3 (10H, m), 8.4-8.5 (1H, m)

30

Preparation 13

The object compound was obtained according to a similar manner to that of Preparation 4.

35 NMR (DMSO- d_6 , δ) : 1.9-2.1 (1H, m), 2.4-2.8 (1H, m), 2.78 and 2.83 (3H, s), 2.85-3.1 (2H, m), 3.15-3.2 and 3.37 (2H, m), 4.2-4.3 (1H, m), 4.45-4.85 (2H, m), 4.9-5.2 (2H, m), 6.73 (2H, s), 7.0-7.4 (12H, m), 9.25 (1H, d, J = 7.6Hz)

Preparation 14

40 To a solution of Starting Compound (8.0 g) and cetyltrimethylammonium chloride (0.58 g) in methylene chloride (120 ml) were added powdered sodium hydroxide (2.5 g) and ethyl bromoacetate (1.66 ml) at room temperature. After stirring the solution overnight, powdered sodium hydroxide (0.5 g) and ethyl bromoacetate (0.88 ml) were added. The mixture was heated under reflux for further four hours. After 45 evaporation of methylene chloride, ethyl acetate (200 ml) was added, and under ice-cooling, 1N-hydrochloric acid was added until the aqueous layer was neutralized to pH 4. The organic layer was washed with diluted sodium hydrogencarbonate solution, 0.5N hydrochloric acid, sodium chloride solution and dried with magnesium sulfate. After concentration, the residue was applied to a silica gel (95 g) column eluting first with methylene chloride then with a mixed solvent of methylene chloride and ethyl acetate (9:1 to 3:2) to 50 give purified Object Compound (3.4 g) as an amorphous solid.

IR (CH_2Cl_2) : 3400, 1745, 1680, 1640 cm^{-1}

NMR (CDCl_3 , δ) : 1.29 (3H, t, J = 7Hz), 1.48 (9H, s), 1.9-2.4 (2H, m), 2.84 and 2.87 (3H, s), 2.85-3.1 (2H, m), 3.4-3.8 and 3.8 (2H, m), 4.0-4.85 (9H, m), 5.18 (1H, m), 6.8-7.4 (10H, m)

55

Preparation 15

The object compound was obtained according to a similar manner to that of Preparation 4.

NMR (DMSO-d₆, δ) : 1.22 (3H, t, J=7Hz), 1.75-2.0 (1H, m), 2.5-2.6 (1H, m), 2.75 and 2.81 (3H, s), 2.9-3.1 (2H, m), 3.25-3.5 (2H, m), 4.14 (2H, q, J=7Hz), 4.20 (2H, s), 4.2-4.6 (4H, m), 4.9-5.05 (1H, m), 7.0-7.4 (10H, m), 8.88 (1H, br s), 9.20 (1H, d, J=7.7Hz), 10.38 (1H, br s)

5

Preparation 16

To a solution of Boc-Asp(OBzl)-OH (3.23 g) and NMM (1.01 g) in methylene chloride (30 ml) was added isobutyl chloroformate (1.37 g) dropwise at -20°C. The solution was stirred at the same temperature for twenty minutes. The solution was cooled to -35°C and was added to a solution of Starting Compound (3.05 g) and NMM (1.01 g) in methylene chloride (20 ml). The mixture was stirred for an hour, raising the temperature gradually to 0°C, and further stirred under ice cooling for half an hour. After concentration, the product was extracted with ethyl acetate and the organic layer was washed with water, diluted sodium hydrogencarbonate solution, 0.5N hydrochloric acid, and sodium chloride solution, and dried over magnesium sulfate. After concentration and crystallization with a mixed solvent of diethyl ether and IPE under ice-cooling gave Object Compound (3.97 g).

mp : 56-57°C

IR (Nujol) : 3300, 1736, 1690, 1660, 1640 (sh), 1630, 1515 cm⁻¹

NMR (CDCl₃, δ) : 1.48 (9H, s), 2.58 (2H, s), 2.8-3.17 (5H, m), 4.2 (1H, m), 4.4-4.7 (2H, m), 5.17 (2H, s), 5.2

20 (1H, m), 5.58 (1H, d, J=8Hz), 7.1 (1H, m), 7.2-7.5 (15H, m)

Preparation 17

25 To a solution of Boc-Asp(OBzl)-OH (0.97 g), Starting Compound (0.914 g) and HOBT (0.405 g) in a mixed solvent of methylene chloride (25 ml) and DMF (5 ml) was added WSC (0.511 g) under ice-cooling. The solution was stirred at the same temperature for three hours. After concentration the product was extracted with ethyl acetate. The organic layer was washed successively with water, diluted sodium hydrogencarbonate solution, 0.5N hydrochloric acid, sodium chloride solution, and dried over magnesium sulfate. Concentration gave a crude product (1.72 g), which was purified on a silica gel column eluting with chloroform-ethyl acetate (4:1) to give Object Compound (1.88 g).

Preparation 18

35 A mixture of Starting Compound (1.0 g) and anisole (1.0 ml) was treated with TFA (15 ml) under ice-cooling for fifteen minutes and further at room temperature for twenty minutes. After concentration of the mixture, 4N-HCl/DOX (0.85 ml) was added and concentrated again. The residue was washed with n-hexane and IPE four times respectively and the powder was filtered, washed with IPE and dried under vacuum to give Object Compound (0.87 g). The product was used in the next reaction without purification.

Preparation 19

45 To an ice-cooled solution of Starting Compound (2.81 g), HOBT (1.35 g) and N-(2-pyridylmethyl)-N-methylamine (1.22 g) in methylene chloride (28 ml) was added WSC·HCl (1.82 g). The solution was stirred at room temperature for four hours and washed successively with 5% sodium hydrogencarbonate solution, sodium chloride solution and was dried over magnesium sulfate. Evaporation and purification on a silica gel column (84 g) eluting with chloroform-methanol (20:1) gave Object Compound (3.14 g) as an oil.

50 IR (Neat) : 3300, 1700, 1640, 1510, 1245, 1165, 850 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.27 (s) and 1.35 (s)(9H), 2.8-3.0 (2H, m), 2.82 (s) and 2.98 (s)(3H), 4.4-4.9 (3H, m), 8.5-8.7 (2H, m), 8.8-7.4 (5H, m), 7.8-7.8 (1H, m), 8.48 (d, J=4Hz) and 8.53 (d, J=4Hz)(1H), 9.14 (s) and 9.22 (s)(1H)

55

Preparation 20

To an ice-cooled solution of Starting Compound (3.9 g) and anisole (3.9 ml) in methylene chloride (40

ml) was added TFA (25 ml). The solution was stirred for half an hour at room temperature. After evaporation, addition and re-evaporation of 4N-HCl/DOX (5 ml) were repeated twice. The residue was extracted with ethyl acetate and the organic layer was washed successively with saturated sodium hydrogencarbonate solution and brine, and dried over anhydrous magnesium sulfate to give the above intermediate (3.03 g). To the solution in DMF (50 ml) containing Intermediate obtained was added Boc-Pro-OH (2.15 g), HOBT (1.35 g) and WSC·HCl (1.92 g). The solution was stirred for one and half an hour at room temperature. After evaporation and extraction with ethyl acetate. The organic layer was washed successively with water, 1N hydrochloric acid, water, 5% sodium hydrogencarbonate, water and saturated sodium chloride and dried over magnesium sulfate. The evaporated residue was subjected to column chromatography on silica gel (120 g) and eluted with a mixture of ethyl acetate and toluene (1:3). The fractions containing the object compound were combined and evaporated. The residue was collected by filtration, and dried to give Object Compound (4.34 g).

IR (Neat) : 3300, 1690, 1640 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.21 (s) and 1.36 (s)(9H), 1.4-1.8 (3H, m), 1.8-2.1 (1H, m), 2.5-3.1 (4H, m), 3.1-3.4 (2H, m), 3.4-3.7 (2H, m), 4.0-4.1 (1H, m), 4.4-4.8 (2H, m), 4.9-5.1 (1H, m), 7.0-7.3 (9H, m), 8.1-8.3 (1H, m)

Preparation 21

20 The object compounds were obtained according to a similar manner to that of Preparation 4 or 18.

(1) IR (CHCl_3) : 1735, 1685, 1875, 1655, 1640, 1625, 1580, 1545, 1490, 1450 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.78 (s) and 2.88 (s)(3H), 2.9-3.2 (2H, m), 3.2-3.4 (1H, m), 3.5-3.7 (1H, m), 4.2-4.8 (4H, m), 4.8-5.1 (1H, m), 5.5-5.8 (1H, m), 6.9-7.2 (9H, m), 8.84 (br s) and 10.06 (br s)(1H), 9.18 (1H, d, J = 8Hz)

25 (2) IR (CHCl_3) : 1780-1740, 1680, 1655, 1640, 1585, 1545, 1490, 1315 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.6-1.8 (1H, m), 2.1-2.4 (1H, m), 2.81 (s) and 2.93 (s)(3H), 2.9-3.2 (2H, m), 3.2-3.5 (2H, m), 4.2-4.8 (4H, m), 5.08 (1H, q, J = 7Hz), 5.57 (1H, br s), 6.9 (1H, d, J = 7Hz), 7.0-7.8 (8H, m), 8.81 (br s) and 10.80 (br s)(1H), 9.1-9.3 (1H, m)

(3) IR (CHCl_3) : 1875, 1640, 1630, 1590, 1585, 1545, 1490 cm^{-1}

30 NMR (DMSO- d_6 , δ) : 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.78 (s) and 2.85 (s)(3H), 2.9-3.2 (3H, m), 3.2-3.4 (1H, m), 4.2-4.8 (4H, m), 4.8-5.1 (1H, m), 5.5-5.8 (1H, m), 6.9-7.4 (10H, m), 9.20 (1H, d, J = 7Hz)

(4) IR (Nujol) : 3220, 3060, 2820, 1870, 1845, 1580, 1555, 1455 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.6-2.0 (3H, m), 2.2-2.4 (1H, m), 2.78 (s) and 2.83 (s)(3H), 2.9-3.1 (2H, m), 3.1-3.3 (2H, m), 4.1-4.3 (1H, m), 4.3-4.7 (2H, m), 4.8-5.1 (1H, m), 7.0-7.4 (10H, m), 8.3-8.7 (br s) and 9.9-10.3 (br s)(1H), 9.13 (1H, d, J = 8Hz)

(5) IR (CHCl_3) : 3850-3300, 1855, 1640, 1586, 1490, 1455 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.82 (s) and 2.70 (s)(3H), 2.9-3.3 (2H, m), 4.3-4.7 (3H, m), 7.1-7.4 (9H, m), 8.53 (2H, s)

(6) IR (CHCl_3) : 1855, 1605, 1580, 1510, 1495, 1455, 1365, 1315 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.86 (s) and 2.70 (s)(3H), 2.9-3.1 (1H, m), 3.1-3.3 (1H, m), 3.5-3.9 (1H, m), 4.3-4.8 (2H, m), 7.49 (1H, d, J = 7Hz), 7.2-7.7 (7H, m), 7.72 (1H, d, J = 7Hz), 8.84 (2H, s)

(7) mp : 94-105 $^{\circ}\text{C}$

IR (Nujol) : 3460, 1650, 1630, 1590, 1470, 1275 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.59 (s) and 2.87 (s)(3H), 2.9-3.1 (1H, m), 3.1-3.3 (1H, m), 4.3-4.7 (3H, m), 6.9-7.2 (9H, m), 8.53 (2H, s)

45 (8) NMR (DMSO- d_6 , δ) : 2.74 (s) and 2.81 (s)(3H), 2.8-3.1 (2H, m), 3.6-3.9 (3H, m), 4.46 (2H, dd, J = 15 and 20Hz), 4.9-5.1 (1H, m), 5.52 (1H, broad s), 7.0-7.4 (10H, m), 8.29 (3H, broad s), 9.0-9.1 (1H, m)

(9) NMR (DMSO- d_6 /D₂O, δ) : 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.7-3.5 (7H, m), 4.2-4.5 (2H, m), 4.6-5.0 (3H, m), 6.85 (d, J = 8Hz) and 6.70 (d, J = 8Hz)(2H), 6.96 (d, J = 8Hz) and 7.07 (d, J = 8Hz)(2H), 7.34 (1H, d, J = 8Hz), 7.61 (t, J = 8Hz), and 7.83 (t, J = 8Hz)(1H), 8.08 (t, J = 8Hz) and 8.35 (t, J = 8Hz)(1H), 8.71 (d, J = 4Hz) and 8.78 (d, J = 4Hz)(1H)

50 (10) NMR (DMSO- d_6 , δ) : 1.7-1.9 (1H, m), 2.2-2.4 (1H, m), 2.8-3.4 (7H, m), 4.2-4.5 (2H, m), 4.75 (1H, d, J = 16Hz), 4.87 (1H, d, J = 16Hz), 4.98 (1H, q, J = 8Hz), 7.2-7.35 (8H, m), 7.40 (1H, d, J = 8Hz), 7.62 (t, J = 8Hz) and 7.83 (t, J = 8Hz)(1H), 8.10 (t, J = 8Hz) and 8.37 (t, J = 8Hz)(1H), 8.61 (1H, broad), 8.70 (d, J = 5Hz) and 8.78 (d, J = 5Hz)(1H), 9.23 (1H, d, J = 7Hz), 10.20 (1H, broad)

(11) IR (CHCl_3) : 1740, 1680, 1640, 1550, 1495 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.7-1.9 (1H, m), 1.83 (s) and 1.95 (s)(3H), 2.2-2.4 (1H, m), 2.8-3.2 (3H, m), 3.2-3.6 (3H, m), 3.8-4.1 (2H, m), 4.2-5.1 (5H, m), 5.57 (1H, s), 7.0-7.4 (11H, m), 9.20 (1H, t, J = 8Hz)

Preparation 22

The object compounds were obtained according to a similar manner to that of Preparation 3 or 17.

(1) mp : 112-113 °C

5 IR (Nujol) : 3370, 3310, 1700, 1690 (sh), 1660, 1645, 1630, 1538, 1525 (sh), 1285, 1260, 1175 cm^{-1}
 NMR (CDCl_3 , δ) : 1.41 (9H, s), 1.2-1.8 (6H, m), 2.60 and 2.78 (3H, s), 2.85-3.2 (4H, m), 3.9-4.7 (3H, m), 4.9-5.35 (5H, m), 6.8-7.4 (16H, m)

10

	Elemental Analysis. Calculated for $\text{C}_{36}\text{H}_{46}\text{N}_4\text{O}_6$:
	C 68.55, H 7.35, N 8.88 Found : C 68.90, H 6.96, N 8.88

15 (2) NMR (CDCl_3 , δ) : 1.3-1.9 (8H, m), 1.43 (9H, s), 2.65 and 2.83 (3H, s), 3.0-3.4 (4H, m), 3.9-4.3 (2H, m), 4.33 and 4.65 (ABq, 2H, J = 14Hz), 5.0-5.4 (3H, m), 5.20 (2H, s), 6.8-7.5 (14H, m)
 (3) NMR (CDCl_3 , δ) : 1.45 (9H, s), 1.5-2.1 (4H, m), 2.68 and 2.79 (3H, s), 2.92-3.4 (4H, m), 4.0-4.3 (1H, m), 4.43 (2H, ABq, J = 15Hz), 5.08 (2H, s), 4.9-5.3 (3H, m), 6.8-7.4 (15H, m)

20

Preparation 23

25 The object compounds were obtained according to a similar manner to that of Preparation 4 or 18.

(1) - (4)

30 The products were used in the next reaction without purification.

Preparation 24

35 The object compound was obtained according to a similar manner to that of Preparation 2 or 4.

IR (Nujol) : 2700, 2450, 1640 cm^{-1}
 NMR ($\text{DMSO-}d_6$, δ) : 2.47 (3H, s), 2.51 (3H, s), 2.7-3.8 (2H, m), 4.40 (2H, s), 4.84 (1H, dd, J = 6 and 9Hz), 6.8-7.4 (10H, m), 9.5 (2H, br s)

40 Preparation 25

The object compounds were obtained according to a similar manner to that of Preparation 19.

(1) IR (Neat) : 3320, 2980, 1720, 1705, 1690, 1655, 1640, 1580, 1490 cm^{-1}
 NMR ($\text{DMSO-}d_6$, δ) : 1.24 (s) and 1.35 (s)(9H), 2.74 (s) and 2.88 (s)(3H), 2.7-3.0 (2H, m), 4.30 (1H, d, J = 15Hz), 4.5-4.7 (2H, m), 6.8-7.4 (10H, m)
 (2) IR (CHCl_3) : 3300, 2950, 1705, 1645, 1490, 1385, 1315 cm^{-1}
 NMR ($\text{DMSO-}d_6$, δ) : 1.18 and 1.38 (s)(9H), 2.7-3.2 (2H, m), 2.91 (s) and 2.94 (s)(3H), 4.3-4.5 (1H, m), 4.6-4.9 (2H, m), 7.0-7.8 (10H, m)
 (3) IR (Neat) : 3320, 2980, 1705, 1640, 1490, 1455, 1385 cm^{-1}
 NMR ($\text{DMSO-}d_6$, δ) : 1.23 (s) and 1.34 (s)(3H), 2.7-3.0 (5H, m), 4.4-4.7 (3H, m), 7.0-7.4 (11H, m)
 (4) IR (Neat) : 3300, 1710, 1640, 1170 cm^{-1}
 NMR ($\text{DMSO-}d_6$, δ) : 1.24 (s) and 1.34 (s)(9H), 2.7-3.0 (2H, m), 2.84 (s) and 2.89 (s)(3H), 4.4-4.8 (3H, m), 6.8-7.3 (8H, m), 7.8-7.8 (1H, m), 8.49 (d, J = 4Hz) and 8.54 (d, J = 4Hz)(1H)
 (5) IR (Nujol) : 3400, 3380, 1690, 1625, 1520 cm^{-1}
 NMR ($\text{DMSO-}d_6$, δ) : 1.25 (s) and 1.32 (s)(9H), 2.6-3.8 (6H, m), 4.2-4.9 (4H, m), 6.8-7.4 (11H, m)

Preparation 26

The object compound was obtained according to a similar manner to that of Preparation 1.
mp : 74-75 °C

IR (Nujol) : 1680, 1645 cm⁻¹

5 NMR (DMSO-d₆, δ) : 0.94 (s), 1.12 (s) and 1.27 (s)(9H), 2.6-3.1 (2H, m), 2.71 (3H, s), 2.82 (3H, s), 4.2-4.7 (2H, m), 4.8-5.4 (1H, m), 6.9-7.4 (10H, m)

Preparation 27

10 The object compound was obtained according to a similar manner to that of Example 27.

NMR (DMSO-d₆, δ) : 1.39 (9H, s), 2.5 (2H, m), 2.74 and 2.79 (3H, s), 2.8-3.0 (2H, m), 4.1-4.4 (1H, m), 4.48 (2H, s), 4.8-5.1 (1H, m), 7.0-7.4 (11H, m), 8.04 (1H, d, J = 8Hz), 12.21 (1H, s)

15 Preparation 28

The object compound was obtained according to a similar manner to that of Preparation 6.

mp : 191-193 °C

IR (Nujol) : 3320, 1730, 1680 cm⁻¹

20 NMR (DMSO-d₆, δ) : 1.2-1.4 (1H, m), 1.39 (9H, s), 1.5-1.7 (1H, m), 1.7-1.9 (1H, m), 1.9-2.2 (1H, m), 2.8-3.1 (1H, m), 3.7-3.8 (2H, m), 4.5-4.8 (2H, m), 12.7 (1H, broad)

Preparation 29

25

The object compounds were obtained according to a similar manner to that of Preparation 3 or 17.
(1) IR (Neat) : 3350 (broad), 1690-1630 cm⁻¹

NMR (DMSO-d₆, δ) : 1.2-1.5 (2H, m), 1.33 (9H, s), 1.8-1.8 (1H, m), 1.8-2.1 (1H, m), 2.8-3.2 (6H, m), 3.6-3.8 (2H, m), 4.3-4.7 (4H, m), 4.8-5.1 (1H, m), 7.0-7.1 (2H, m), 7.1-7.4 (8H, m), 8.1-8.2 (1H, m)

30

(2) mp : 115-116 °C

IR (Nujol) : 1690, 1645 cm⁻¹

NMR (DMSO-d₆, δ) : 1.29 (s), 1.30 (s), 1.38 (s) and 1.39 (s)(9H), 1.5-1.9 (3H, m), 2.0-2.3 (1H, m), 2.5-2.9 (1H, m), 2.72 (s) and 2.77 (s)(3H), 3.00 (3H, s), 3.2-3.5 (3H, m), 4.3-4.7 (3H, m), 5.4-5.7 (1H, m), 6.8-6.9 (1H, m), 7.0-7.1 (1H, m), 7.1-7.4 (8H, m)

35

40

Elemental Analysis. Calculated for C ₂₈ H ₃₇ N ₂ O ₄ :	
Found :	C 70.12, H 7.78, N 8.78 C 69.93, H 7.81, N 8.70

(3) IR (CHCl₃) : 3350, 3000, 1700-1640, 1530, 1495, 1410, 1320 cm⁻¹

45 NMR (DMSO-d₆, δ) : 1.21 (s), 1.25 (s), 1.33 (s) and 1.39 (s)(9H), 1.5-1.8 (1H, m), 1.8-2.1 (1H, m), 2.7-3.1 (5H, m), 3.1-3.3 (1H, m), 3.3-3.5 (1H, m), 4.0-4.3 (2H, m), 4.4-4.7 (2H, m), 4.9-5.2 (2H, m), 6.8-7.8 (8H, m), 7.7-7.8 (1H, m), 8.3-8.5 (1H, m)

(4) IR (CHCl₃) : 3430, 3320, 3000, 1690-1620, 1585, 1525, 1480 cm⁻¹

NMR (DMSO-d₆, δ) : 1.25 (s) and 1.38 (s)(9H), 1.5-1.8 (1H, m), 1.8-2.1 (1H, m), 2.78 (s) and 2.87 (s)(3H), 2.7-3.1 (2H, m), 3.1-3.3 (1H, m), 3.3-3.5 (1H, m), 4.1-4.3 (2H, m), 4.3-4.8 (2H, m), 4.8-5.0 (2H, m), 6.8-7.0 (2H, m), 7.0-7.4 (7H, m), 8.3-8.4 (1H, m)

(5) IR (CHCl₃) : 3600-3250, 1695, 1680, 1645, 1490, 1455 cm⁻¹

NMR (DMSO-d₆, δ) : 1.24 (s) and 1.38 (s)(9H), 1.5-1.8 (1H, m), 1.8-2.1 (1H, m), 2.7-3.1 (m) and 2.91 (s)(5H), 3.1-3.3 (1H, m), 3.3-3.5 (1H, m), 4.1-4.3 (2H, m), 4.3-4.8 (2H, m), 4.9-5.1 (2H, m), 6.8-7.4 (8H, m), 8.2-8.4 (1H, m)

55

(6) IR (Neat) : 3330, 3000, 2950, 1700, 1640, 1400 cm⁻¹

NMR (DMSO-d₆, δ) : 1.25 (s) and 1.39 (s)(9H), 1.5-1.8 (1H, m), 2.0-2.3 (1H, m), 2.78 (s) and 2.85 (s)(3H), 2.8-3.1 (2H, m), 3.18 (s) and 3.19 (s)(3H), 3.4-3.5 (2H, m), 3.8-3.9 (1H, m), 4.0-4.2 (1H, m), 4.4-4.8 (2H, m), 4.8-5.1 (1H, m), 7.0-7.3 (10H, m), 8.37 (1H, d, J = 8Hz)

(7) IR (Neat) : 3310, 1715, 1840, 1495 cm^{-1}
 NMR (DMSO-d₆, δ) : 1.08 (d, J = 7Hz) and 1.11 (d, J = 7Hz)(3H), 1.37 (9H, s), 2.72 (s) and 2.79 (s)(3H), 2.8-3.1 (2H, m), 3.8-4.1 (1H, m), 4.44 (s) and 2.47 (s)(2H), 4.8-5.1 (1H, m), 6.8-7.0 (1H, m), 7.0-7.4 (10H, m), 8.1-8.2 (1H, m)

8 (8) IR (Neat) : 3330, 1715, 1845, 1630, 1495 cm^{-1}
 NMR (DMSO-d₆, δ) : 0.9-1.0 (3H, m), 1.39 (9H, s), 2.72 (s) and 2.79 (s)(3H), 2.8-3.1 (2H, m), 3.7-3.9 (2H, m), 4.3-4.8 (2H, m), 4.7-4.8 (1H, m), 4.9-5.1 (1H, m), 6.41 (1H, d, J = 8Hz), 7.0-7.3 (10H, m), 8.1-8.3 (1H, m)

(9) NMR (DMSO-d₆, δ) : 1.38 (9H, s), 1.8-1.8 (2H, m), 2.3-2.4 (2H, m), 2.73 and 2.80 (3H, s), 2.8-3.1 (2H, m), 3.8-4.1 (1H, m), 4.3-4.5 (2H, m), 4.9-5.1 (1H, m), 6.9-7.35 (11H, m), 8.1-8.25 (1H, m)

10 (10) IR (Neat) : 1710, 1640, 1490, 1170 cm^{-1}
 NMR (DMSO-d₆, δ) : 1.30 (s) and 1.37 (s)(9H), 2.8-3.8 (10H, m), 4.3-4.7 (5H, m), 5.5-5.7 (1H, m), 6.7-7.4 (16H, m)

(11) IR (Neat) : 3320, 2980, 1720, 1640 cm^{-1}
 NMR (DMSO-d₆, δ) : 0.96 (s), 1.04 (s), 1.05 (s) and 1.08 (s)(9H), 2.8-3.5 (4H, m), 2.75 (s) and 2.77 (s)(3H), 3.02 (s) and 3.05 (s)(3H), 4.1-4.8 (3H, m), 5.03 (2H, s), 5.57 (1H, t, J = 7Hz), 6.8-7.6 (16H, m)

Preparation 30

20 The object compounds were obtained according to a similar manner to that of Preparation 20.
 (1) IR (Neat) : 1690-1630, 1510, 1405, 1180 cm^{-1}
 NMR (DMSO-d₆, δ) : 1.28 (s) and 1.39 (s)(9H), 1.5-2.1 (2H, m), 2.7-3.0 (5H, m), 3.2-3.5 (2H, m), 4.0-4.3 (2H, m), 4.3-5.1 (4H, m), 6.5-6.7 (2H, m), 6.7-7.4 (6H, m), 7.8-7.8 (1H, m), 8.1-8.3 (1H, m), 8.47 (d, J = 4Hz) and 8.54 (d, J = 4Hz)(1H), 9.14 (s) and 9.23 (s)(1H)

25 (2) IR (Neat) : 1690-1650, 1640, 1405, 1180 cm^{-1}
 NMR (DMSO-d₆, δ) : 1.24 (s) and 1.39 (s)(9H), 1.5-2.1 (2H, m), 2.8-3.2 (5H, m), 3.2-3.5 (2H, m), 4.0-4.3 (2H, m), 4.4-5.1 (4H, m), 6.8-7.4 (7H, m), 7.8-7.8 (1H, m), 8.2-8.4 (1H, m), 8.48 (d, J = 5Hz) and 8.55 (d, J = 5Hz)-(1H)

(3) IR (CHCl₃) : 1740, 1705-1630, 1525 cm^{-1}

30 NMR (DMSO-d₆, δ) : 1.22, 1.24 and 1.39 (9H, s), 1.5-2.1 (2H, m), 1.89 and 1.92 (3H, s), 2.8-3.1 (2H, m), 3.1-3.8 (4H, m), 3.8-4.0 (2H, m), 4.1-4.2 (2H, m), 4.4-5.1 (4H, m), 7.0-7.4 (10H, m), 8.3-8.5 (1H, m)

Preparation 31

35 The object compound was obtained according to a similar manner to that of Example 28.
 mp : 172-175 °C
 IR (Nujol) : 3320, 3200, 1693, 1690 (sh), 1645, 1530 cm^{-1}

40

Preparation 32

The object compound was obtained according to a similar manner to that of Example 35.

45 IR (Neat) : 3330, 2980, 1745, 1710, 1640, 1235, 1170 cm^{-1}
 NMR (DMSO-d₆, δ) : 1.27 (s) and 1.33 (s)(9H), 1.93 (3H, s), 2.8-3.1 (2H, m), 3.3-3.9 (2H, m), 3.9-4.2 (2H, m), 4.4-4.7 (3H, m), 7.0-7.4 (11H, m) :

Preparation 33

The object compound was obtained according to a similar manner to that of Example 38.
 IR (Neat) : 3400, 2980, 1640, 1490 cm^{-1}
 NMR (DMSO-d₆, + D₂O, δ) : 0.97 (s), 1.05 (s), 1.08 (s) and 1.09 (s)(9H), 2.8-2.9 (1H, m), 2.77 (3H, br s), 2.98 (s) and 3.03 (s)(3H), 3.2-3.4 (3H, m), 3.7-3.9 (1H, m), 4.1-4.9 (2H, m), 5.5-5.8 (1H, m), 6.8-7.4 (10H, m)

Preparation 34

To an ice-cooled solution of Starting Compound (2.31 g) and methyl iodide (5 ml) in THF (30 ml) was added sodium hydride (60% in oil, 1.2 g) under atmosphere of nitrogen. The mixture was stirred for one and half an hour at the same temperature and for nine hours at room temperature. Ether and water were added to the reaction mixture and the aqueous layer was separated. After acidification with 6N hydrochloric acid, the aqueous layer was extracted with ethyl acetate twice. The extract was washed successively with water and sodium chloride solution and was dried over magnesium sulfate. Evaporation of the extract gave Object Compound (2.64 g) as an oil.

5 acid, the aqueous layer was extracted with ethyl acetate twice. The extract was washed successively with water and sodium chloride solution and was dried over magnesium sulfate. Evaporation of the extract gave Object Compound (2.64 g) as an oil.

10 IR (Neat) : 3000, 2850, 1740, 1700, 1400, 1160 cm^{-1}
 NMR (DMSO-d₆, δ) : 1.34 (s) and 1.39 (s)(9H), 1.9-2.0 (1H, m), 2.2-2.4 (1H, m), 3.21 (3H, s), 3.3-3.5 (2H, m),
 10 3.9-4.1 (2H, m), 12.55 (1H, br)

Example 1

15 Starting Compound (885 mg) was treated in TFA (15 ml) under ice-cooling for ten minutes and at room temperature for ten minutes. After concentration, the residue was dissolved in methylene chloride (30 ml), and under cooling, a solution of sodium hydrogencarbonate was added until aqueous layer was neutralized to pH 7. The organic layer was separated, washed with sodium chloride solution and dried over anhydrous magnesium sulfate to give the intermediate. After filtration, BSA (0.905 g) was added to the filtrate, and under ice-cooling, indole-3-carbonyl chloride (384 mg) was added. The solution was stirred for half an hour and concentrated. The residue was dissolved in a mixture of THF (15 ml) and 1N hydrochloric acid (5 ml), and the solution was stirred for half an hour. Ethyl acetate and water were added to the solution and the separated organic layer was washed with water, diluted sodium hydrogencarbonate solution, and sodium chloride solution, and dried over magnesium sulfate. After concentration, the residue was dissolved in chloroform and subjected to a silica gel column chromatography and eluted first with ethyl acetate and then with chloroform-methanol (4:1). The main fraction was concentrated and the residue was triturated with ether, filtered, and dried to give Object Compound (883 mg).

20 IR (Nujol) : 3250, 1630, 1590 (sh), 1530 cm^{-1}
 NMR (DMSO-d₆, δ) : 1.7-2.1 (2H, m), 2.65-3.1 (7H, m), 3.65 (d, $J = 10\text{Hz}$) and 3.8 (m)(2H), 4.2-4.6 (3H, m),
 25 4.7 (1H, m), 4.8-5.05 (2H, m), 6.9-7.3 (12H, m), 7.45 (1H, d, $J = 7\text{Hz}$), 7.85 (1H, br), 8.03 (1H, d, $J = 7\text{Hz}$), 8.4 (1H, m), 11.84 (1H, s)

35 Elemental Analysis. Calculated for
 $\text{C}_{31}\text{H}_{32}\text{N}_4\text{O}_4 \cdot 1/2\text{H}_2\text{O}$:

Found :	C 89.78, H 6.23, N 10.50 C 89.40, H 6.19, N 10.39
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40

Example 2

45 Starting Compound (1.02 g) was treated with TFA (15 ml) under ice-cooling for 15 minutes and at room temperature for 10 minutes. After concentration, the residue was dissolved in methylene chloride (50 ml), and under cooling, sodium hydrogencarbonate solution was added until the aqueous layer was neutralized to pH 7. The organic layer was separated, washed with sodium chloride solution, and dried over anhydrous magnesium sulfate. After filtration, indole-2-carboxylic acid (387 mg), HOBT (324 mg) was added, and under ice-cooling, WSC[®]HCl (458 mg) was added. The mixture was stirred at the same temperature for two hours and at room temperature overnight. The solution was concentrated and the product was extracted with ethyl acetate. The organic layer was washed successively with water diluted sodium hydrogencarbonate solution, 0.5N hydrochloric acid, and sodium chloride solution and dried over anhydrous magnesium sulfate. After concentration, the residue was applied to a silica gel column chromatography and eluted first with chloroform and then with chloroform-methanol (100:8). The main fraction was concentrated and the residue was triturated with diisopropyl ether, filtered, and dried to give Object Compound (840 mg).

50 IR (Nujol) : 3250, 1630, 1595, 1525 cm^{-1}
 NMR (DMSO-d₆, δ) : 1.7-2.2 (2H, m), 2.72 and 2.79 (3H, s), 2.8-3.2 (2H, m), 3.7-3.9 (1H, m), 4.0-4.2 (1H, m),
 55 4.3-4.8 (3H, m), 4.8-4.8 (1H, m), 4.9-5.2 (2H, m), 6.9-7.3 (13H, m), 7.48 (1H, d, $J = 8\text{Hz}$), 7.87 (1H, d,

J = 8Hz), 8.5-8.6 and 8.76 (1H, m), 11.47 and 11.57 (1H, s)

6

Elemental Analysis. Calculated for C ₃₁ H ₃₂ N ₄ O ₆ :	
Found :	C 70.97, H 6.15, N 10.68
	C 69.75, H 6.11, N 10.74

10

Example 3

15 To an ice-cooled solution of Starting Compound (1.13 g) in methylene chloride (5 ml) was added TFA (13 ml). The solution was stirred at the same temperature for 15 minutes and at room temperature for another 15 minutes. The solution was concentrated and the residue was dissolved in methylene chloride (3 ml). Sodium hydrogencarbonate solution was added until the aqueous layer was neutralized to pH 7. The organic layer was separated, washed with sodium chloride solution, and dried over magnesium sulfate. After filtration, under ice-cooling, TEA (0.473 g) and trans-cinnamoyl chloride (391 mg) were added to the solution. After stirring for half an hour, the solution was concentrated and the product was extracted with ethyl acetate. The organic layer was washed successively with water, diluted sodium hydrogencarbonate solution, 0.5N hydrochloric acid, and sodium chloride solution, and dried over anhydrous magnesium sulfate. After concentration, the residue was applied to a silica gel column chromatography and eluted successively with methylene chloride, methylene chloride-acetate (10:1 to 3:1, gradient), and methylene chloride-acetone-methanol (70:30:2). The main fraction was pooled and concentrated, and the residue was triturated with ether, filtered, and dried to give Object Compound (0.737 g) as an amorphous solid.
 IR (Nujol) : 3250, 1640, 1595, 1080, 975 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.7-2.2 (2H, m), 2.63-2.73 and 2.79 (3H, s), 2.8-3.1 (2H, m), 3.5-3.9 (2H, m), 4.2-4.8 (4H, m), 4.9-5.2 (2H, m), 6.70 (dd, J = 15.4Hz and 4.5Hz) and 6.85-7.8 (m)(15H), 8.4-8.46 and 8.86-8.95 (1H, m)

30

Example 4

35 To an ice-cooled solution of Starting Compound (1.0 g), 3-indoleacetic acid (0.419 g) and HOBT (0.323 g) in methylene chloride (30 ml), was added WSC (0.372 g). The solution was stirred at the same temperature for two hours. Then stirring was continued at room temperature for three hours, during which period, TEA (0.16 ml) and WSC-HCl (229 mg) were added to the solution. The solution was concentrated and the product was extracted with ethyl acetate. The organic layer was washed successively with water, diluted sodium hydrogencarbonate solution, 0.5N hydrochloric acid, and sodium chloride solution, and dried over anhydrous magnesium sulfate. After concentration, the residue was applied to a silica gel column chromatography and eluted first with chloroform and then with chloroform-methanol (100:2 to 100:7, gradient elution). The main fraction was concentrated and the residue was triturated with ether, filtered, and dried to give Object Compound (850 mg).
 IR (Nujol) : 3430 (sh), 3300, 1645 (sh), 1630 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.75-2.0 and 2.0-2.2 (2H, m), 2.70-3.2 (5H, m), 3.3-3.45 (2H, m), 3.7 (2H, s), 4.1-4.3 (1H, m), 4.35-4.80 (3H, m), 4.9-5.1 (2H, m), 6.9-7.8 (15H, m), 8.3-8.4 and 8.8-8.9 (1H, m), 10.85 and 10.89 (1H, s)

60

Example 5

55 To an ice-cooled solution of Starting Compound (0.80 g) in methylene chloride (20 ml) were added NMM (0.43 ml) and phenylacetyl chloride (0.26 ml). The solution was stirred at the same temperature for an hour and concentrated. The product was extracted with ethyl acetate and the organic layer was successively washed with water, 1N hydrochloric acid, 5% sodium hydrogencarbonate solution, and sodium chloride solution, and dried over anhydrous magnesium sulfate. Filtration and concentration gave Object Compound (0.78 g) as an amorphous solid.

IR (Nujol) : 3290, 1630, 1490 cm^{-1}

NMR (DMSO-d₆, δ) : 1.7-2.2 (2H, m), 2.7-3.4 (7H, m), 3.84 (2H, s), 4.1-4.6 (4H, m), 4.8-5.1 (2H, m), 7.0-7.4 (15H, m), 8.3-8.4 (m) and 8.8-8.9 (m)(1H)

5

Example 6

The object compounds were obtained according to a similar manner to that of Example 1.

(1) NMR (DMSO-d₆, δ) : 1.75-1.85 (2H, m), 1.96-2.05 (2H, m), 2.43 and 2.80 (3H, s), 2.94-3.13 (2H, m), 3.45-3.50 (2H, m), 4.12 and 4.50 (2H, ABq, $J = 10\text{Hz}$), 4.67-4.79 (1H, m), 5.06-5.17 (1H, m), 6.98-7.30 (14H, m), 7.52 (1H, m), 8.13 (1H, m), 10.21 (1H, m)

(2) IR (Nujol) : 3300-3150, 1650, 1630, 1580, 1530 cm^{-1}

NMR (DMSO-d₆, δ) : 1.4-2.1 (4H, m), 2.75-3.1 (7H, m), 3.71 (2H, m), 4.3-4.7 (3H, m), 4.85-5.15 (1H, m), 7.0-7.3 (12H, m), 7.43 (1H, d, $J = 7.5\text{Hz}$), 7.80 (1H, br), 8.08 (1H, d, $J = 7.4\text{Hz}$), 8.4-8.8 (1H, m), 11.60 (1H, s)

18

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Elemental Analysis. Calculated for $C_{31}H_{32}N_4O_3$:	
	C 73.21, H 6.34, N 11.02
Found :	C 73.03, H 6.26, N 11.00

(3) IR (Nujol) : 3250, 1630, 1540 cm^{-1}

NMR (DMSO-d₆, δ) : 2.78 (s) and 2.83 (s)(3H), 2.8-3.1 (2H, m), 3.7-4.0 (2H, m), 4.3-4.8 (2H, m), 4.9-5.1 (1H, m), 7.0-7.3 (12H, m), 7.4-7.5 (1H, m), 8.0-8.2 (3H, m), 8.3-8.5 (1H, m), 11.57 (1H, s)

(4) IR (Nujol) : 3270, 1625, 1535 cm^{-1}

NMR (DMSO-d₆, δ) : 2.72 (s) and 2.81 (s)(3H), 2.8-3.1 (2H, m), 3.6-3.7 (2H, m), 4.3-4.7 (3H, m), 4.82 (1H, t, $J = 8\text{Hz}$), 5.03 (1H, q, $J = 8\text{Hz}$), 7.0-7.3 (12H, m), 7.4-7.5 (1H, m), 7.7-7.80 (1H, m), 8.1-8.2 (2H, m), 8.3-8.4 (1H, m), 11.62 (1H, s)

(5) IR (Nujol) : 3290, 1685, 1630, 1535 cm^{-1}

NMR (DMSO-d₆, δ) : 2.45-2.70 (2H, m), 2.73 (s) and 2.81 (s)(3H), 2.80-3.10 (2H, m), 4.30-4.60 (2H, m), 4.75-5.05 (2H, m), 6.93 (1H, s), 7.00-7.40 (13H, m), 7.40-7.50 (1H, m), 7.95-8.35 (4H, m), 11.63 (1H, s)

(6) IR (Nujol) : 3270, 1630, 1535, 1495 cm^{-1}

NMR (DMSO-d₆, δ) : 1.41 (s) and 1.45 (s)(6H), 2.70 (s) and 2.87 (s)(3H), 2.8-3.1 (2H, m), 4.3-4.7 (2H, m), 4.9-5.1 (1H, m), 7.0-7.4 (12H, m), 7.4-7.5 (1H, m), 7.7-7.9 (2H, m), 8.1-8.2 (2H, m), 11.60 (1H, s)

Example 7

40

The object compounds were obtained according to a similar manner to that of Example 2.

(1) IR (Nujol) : 3250, 1640 (sh), 1630, 1585, 1525 cm^{-1}

NMR (DMSO-d₆, δ) : 1.7-2.2 (2H, m), 2.71 and 2.79 (3H, s), 2.8-3.1 (2H, m), 3.7-4.1 (2H, m), 4.2-4.5 (3H, m), 4.8-4.7 (1H, m), 4.8-5.1 (2H, m), 6.7-7.3 (14H, m), 8.45-8.55 and 8.77 (1H, m), 8.82 (1H, m), 11.17 and 11.27 (1H, s)

(2) IR (Nujol) : 3300, 1645, 1600, 1530 cm^{-1}

NMR (DMSO-d₆, δ) : 1.8-2.2 (4H, m), 2.74 and 2.81 (3H, s), 2.85-3.1 (2H, m), 3.8-4.0 (2H, m), 4.35-4.7 (3H, m), 4.9-5.05 (1H, m), 7.0-7.3 (13H, m), 7.46 (1H, d, $J = 8\text{Hz}$), 7.88 (1H, d, $J = 8\text{Hz}$), 8.48 (d, $J = 8\text{Hz}$) and 8.71 (d, $J = 8\text{Hz}$)(1H), 11.55 (1H, s)

50

Example 8

The object compound was obtained according to a similar manner to that of Example 3.

NMR (DMSO-d₆, δ) : 1.7-2.3 (4H, m), 2.8-3.1 (5H, m), 3.45-3.9 (2H, m), 4.35-4.75 (3H, m), 4.9-5.05 (1H, m), 6.88 (d, $J = 15.4\text{Hz}$), 7.0-7.8 (m)(17H), 8.38 (d, $J = 8.3\text{Hz}$), 8.7-8.8 (m)(1H)

Example 9

The object compounds were obtained according to a similar manner to that of Example 4.

(1) IR (Neat) : 3300, 1630, 1495 cm^{-1}

NMR (DMSO-d₆, δ) : 1.7-2.8 (4H, m), 2.8-3.1 (7H, m), 3.25-3.85 (2H, m), 4.1-4.6 (4H, m), 4.8-5.1 (2H, m), 7.0-7.3 (15H, m), 8.3-8.4 (m) and 8.7-8.8 (m)(1H)

5 (2) IR (Neat) : 3300, 1630, 1495 cm^{-1}

NMR (DMSO-d₆, δ) : 1.8-2.5 (7H, m), 2.5-3.1 (8H, m), 3.2-3.6 (2H, m), 4.1-4.6 (4H, m), 4.9-5.1 (2H, m), 7.0-7.4 (15H, m), 8.3-8.4 (m) and 8.7-8.8 (m)(1H)

(3) IR (Nujol) : 3300, 1680 (sh), 1640, 1605 cm^{-1}

NMR (DMSO-d₆, δ) : 1.85-2.2 (2H, m), 2.7-3.1 (5H, m), 3.2-3.5 (2H, m), 3.55-3.9 (2H, m), 4.2-4.6 (3H, m), 10 4.8-5.2 (2H, m), 5.4-5.55 (1H, m), 6.5-6.7 (3H, m), 7.0-7.4 (13H, m), 8.4 and 8.8 (1H, m)

(4) IR (Nujol) : 3250, 1625, 1210 cm^{-1}

NMR (DMSO-d₆, δ) : 1.7-2.2 (2H, m), 2.7-3.15 (5H, m), 3.3-3.5 (2H, m), 3.55-3.75 (2H, m), 4.2 (1H, m), 4.35-4.6 (3H, m), 4.9-5.1 (2H, m), 8.80 (1H, dd, $J = 9\text{Hz}$, 2Hz), 8.85 (1H, dd, $J = 9\text{Hz}$, 2Hz), 7.0-7.4 (12H, m), 8.35-8.4 and 8.8-8.9 (1H, m), 8.55-8.6 (1H, m), 10.54 and 10.58 (1H, m)

15 (5) IR (Nujol) : 3280, 1630, 1590 cm^{-1}

NMR (DMSO-d₆, δ) : 1.7-2.1 (2H, m), 2.72 (s) and 2.79 (s)(3H), 2.8-3.1 (2H, m), 3.8-4.0 (2H, m), 4.2-4.7 (4H, m), 4.8-5.1 (2H, m), 6.18 (1H, br s), 6.81 (1H, br s), 6.82 (1H, br s), 7.0-7.4 (10H, m), 8.4-8.5 (1H, m), 11.46 (1H, br s)

20

Example 10

The object compounds were obtained according to a similar manner to that of Example 1.

(1) mp : 234-236 °C

25 28 IR (Nujol) : 3440, 3250, 1685, 1630, 1595 cm^{-1}

NMR (DMSO-d₆, δ) : 1.85-1.85 (1H, m), 2.20-2.45 (1H, m), 2.67 (s) and 2.72 (s)(3H), 2.7-3.1 (2H, m), 3.55-3.70 (1H, m), 3.85-4.00 (1H, m), 4.15-4.30 (1H, m), 4.40 (2H, s), 4.55-4.70 (1H, m), 4.80-5.05 (1H, m), 5.28 (1H, br s), 6.80-7.00 (2H, m), 7.00-7.30 (10H, m), 7.44 (1H, d, $J = 7.5\text{Hz}$), 7.88 (1H, s), 8.02 (1H, d, $J = 8\text{Hz}$), 8.45 (1H, d, $J = 8\text{Hz}$), 11.88 (1H, s)

30

Elemental Analysis. Calculated for $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_4$:	
Found :	C 70.97, H 6.15, N 10.68 C 70.88, H 6.08, N 10.60

(2) IR (Nujol) : 3180, 1640, 1590, 1570 cm^{-1}

40 NMR (DMSO-d₆, δ) : 1.8-2.1 (1H, m), 2.3-2.5 (1H, m), 2.74 (s) and 2.84 (s)(3H), 2.8-3.1 (2H, m), 4.1-4.6 (4H, m), 4.8-5.1 (2H, m), 7.0-7.4 (12H, m), 7.4-7.5 (1H, m), 7.78 (1H, s), 8.15 (1H, d, $J = 8\text{Hz}$), 8.5-8.7 (1H, m), 11.74 (1H, s)

(3) IR (Nujol) : 3250, 1630, 1525 cm^{-1}

NMR (DMSO-d₆, δ) : 2.74 (s) and 2.83 (s)(3H), 2.8-3.35 (4H, m), 4.4-4.7 (3H, m), 4.9-5.2 (3H, m), 7.0-7.3 (12H, m), 7.48 (1H, d, $J = 7\text{Hz}$), 7.87 (1H, d, $J = 2\text{Hz}$), 7.94 (1H, d, $J = 7\text{Hz}$), 8.58 (d, $J = 8\text{Hz}$) and 8.60 (d, $J = 8\text{Hz}$)(1H), 11.79 (1H, s)

(4) IR (Nujol) : 3400, 1685, 1240 cm^{-1}

NMR (DMSO-d₆, δ) : 1.7-2.2 (2H, m), 2.67 (s) and 2.75 (s)(3H), 2.8-3.0 (2H, m), 3.8-3.8 (1H, m), 3.8-4.1 (1H, m), 4.2-4.8 (3H, m), 4.8-5.0 (3H, m), 6.58 (d, $J = 8\text{Hz}$), 6.82 (d, $J = 8\text{Hz}$)(2H), 6.8-7.3 (9H, m), 7.44 (1H, d, $J = 7\text{Hz}$), 7.85 (1H, s), 8.03 (1H, d, $J = 7\text{Hz}$), 8.2-8.4 (1H, m), 9.20 (s) and 9.22 (s)(1H), 11.84 (1H, s)

50

Example 11

The object compounds were obtained according to a similar manner to that of Example 4.

55 (1) IR (Nujol) : 3400, 3300, 1640 (sh), 1630, 1570 cm^{-1}

NMR (DMSO-d₆, δ) : 1.7-2.4 (2H, m), 2.59, 2.64, 2.72 and 2.79 (3H, s), 2.8-3.1 (2H, m), 3.68, 3.8-3.9 and 3.95-4.1 (2H, m), 4.25-4.55 (3H, m), 4.8-4.8 (1H, m), 4.9-5.2 (2H, m), 6.8-7.8 (15H, m), 8.58 and 8.76 (2H, two sets of d, $J = 8\text{Hz}$)

5

Elemental Analysis. Calculated for C ₃₁ H ₃₁ N ₃ O ₅ :	
Found :	C 70.84, H 5.94, N 7.99
Found :	C 70.09, H 6.02, N 8.01

(2) IR (Nujol) : 3400, 3220, 1770, 1630, 1615, 1570 cm⁻¹
 10 NMR (DMSO-d₆, δ) : 1.75-2.3 (2H, m), 2.59, 2.72 and 2.79 (3H, s), 2.9-3.1 (2H, m), 3.73 and 4.10 (2H, br s), 4.20-4.55 (3H, m), 4.65-4.8 (1H, m), 4.85-5.1 and 5.3-5.4 (2H, m), 6.8-7.3 (11H, m), 7.4 (1H, m), 7.6 (1H, m), 8.17 (1H, d, J = 8.1Hz), 8.45-8.6 (1H, m)

15

Elemental Analysis. Calculated for C ₃₀ H ₃₃ N ₃ O ₄ :	
Found :	C 68.29, H 6.30, N 13.27
Found :	C 67.20, H 5.93, N 13.33

20

Example 12

25 The object compounds were obtained according to a similar manner to that of Example 2.
 (1) IR (Nujol) : 3200, 1670, 1640, 1605 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.7-2.3 (2H, m), 2.48 (s), 2.57 (s), 2.70 (s) and 2.78 (s)(3H), 2.7-3.0 (2H, m), 3.6-4.5 (5H, m), 4.5-5.4 (3H, m), 6.5-6.7 (2H, m), 6.7-7.1 (4H, m), 7.1-7.3 (4H, m), 7.3-7.5 (1H, m), 7.5-7.7 (1H, m), 8.18 (1H, d, J = 8Hz), 8.37 (d, J = 8Hz) and 8.48 (d, J = 8Hz)(1H), 9.21 (1H, br s), 13.3-13.7 (1H, broad)
 (2) IR (Nujol) : 3250, 1630-1585, 1530, 1510 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.7-2.1 (2H, m), 2.5-3.0 (2H, m), 2.70 (s) and 2.78 (s)(3H), 3.7-3.9 (1H, m), 3.9-4.1 (1H, m), 4.2-4.5 (3H, m), 4.5-5.0 (2H, m), 5.09 (1H, d, J = 2Hz), 6.5-7.1 (9H, m), 7.1-7.3 (4H, m), 8.42 (d, J = 8Hz) and 8.72 (d, J = 8Hz)(1H), 8.81 (1H, s), 9.22 (1H, s), 11.28 (1H, br s)

35

Example 13

40 To a solution of Starting Compound (1.87 g) in methylene chloride (30 ml), 3-chloroperoxybenzoic acid (0.84 g) was added under ice-cooling. After stirring at the same temperature for 15 minutes, 5% sodium hydrogen carbonate solution was added. The mixture was filtered over celite. The organic layer was separated, dried over anhydrous magnesium sulfate and evaporated. The residue was applied to a silica gel column and eluted with a mixture of chloroform and methanol (20:1). The fractions containing the more polar product were collected and evaporated. The residue was pulverized with IPE, filtered and dried to give A-isomer of Object Compound (0.48 g.).
 45 IR (Nujol) : 3250, 1640, 1525, 1040 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.69 (s) and 2.77 (s)(3H), 2.8-3.1 (3H, m), 3.45-3.85 (1H, m), 4.3-4.6 (3H, m), 4.9-5.1 (1H, m), 5.3-5.4 (1H, m), 5.4-5.8 (1H, m), 7.0-7.1 (2H, m), 7.1-7.3 (10H, m), 7.47 (1H, d, J = 7Hz), 7.9-8.0 (2H, m), 8.55-8.65 (1H, m), 11.88 (1H, s)
 The fractions containing the less polar product were collected and evaporated. The residue was 50 crystallized with IPE, filtered and dried to give B-isomer of Object Compound (0.40 g).
 IR (Nujol) : 3500, 3300, 1640, 1610, 1530, 1040 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.72 (s) and 2.78 (s)(3H), 2.75-3.15 (3H, m), 3.25-3.50 (1H, m), 4.3-4.7 (3H, m), 4.9-5.1 (1H, m), 5.1-5.3 (1H, m), 5.40-5.55 (1H, m), 6.95-7.35 (12H, m), 7.49 (1H, d, J = 7Hz), 7.85-7.95 (2H, m), 8.7-8.8 (1H, m), 11.82 (1H, s)

55

Example 14

To a solution of Starting Compound (0.5 g) in methylene chloride (10 ml), 3-chloroperoxybenzoic acid (0.4 g) was added. After stirring at room temperature for 40 minutes, 3-chloroperoxybenzoic acid (0.2 g) was added and the mixture was warmed at 38 °C for half an hour. After adding 5% sodium hydrogencarbonate solution, the mixture was filtered over Celite. The organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and evaporated. The residue was applied to a silica gel column and eluted with a mixture of chloroform and methanol (30:1). The main fractions were collected and evaporated. The residue was pulverized with IPE, filtered and dried to give Object Compound (0.26 g).
 5 IR (Nujol) : 3280, 1830, 1525 cm^{-1}
 NMR (DMSO- d_6 , δ) : 2.74 (s) and 2.80 (s)(3H), 2.8-3.3 (3H, m), 3.8-3.8 (1H, m), 4.4-4.5 (2H, m), 4.6-4.8 (1H, m), 4.9-5.1 (1H, m), 5.2-5.3 (1H, m), 5.4-5.5 (1H, m), 7.0-7.3 (12H, m), 7.48 (1H, d, J = 7.5Hz), 7.9-8.0 (2H, m), 8.7-8.8 (1H, m), 11.94 (1H, s)

Example 15

15 To a mixture of Starting Compound (5.0 g), cetyltrimethylammonium chloride (313 mg), and powdered sodium hydroxide (1.52 g) in methylene chloride (100 ml) was added tert-butyl bromoacetate (1.88 g) under ice cooling. The mixture was stirred at the same temperature for an hour.
 20 To the mixture was added 1N-hydrochloric acid (25 ml) and methylene chloride was evaporated. Ethyl acetate and water were added to the residue and the mixture was acidified to pH 3 with 1N hydrochloric acid and was separated. The aqueous layer was extracted with ethyl acetate again and the combined organic layer was washed successively with water, diluted sodium hydrogencarbonate solution, sodium chloride solution and dried with magnesium sulfate. After concentration, the residue was chromatographed on a silica gel column (120 g) eluting with chloroform-methanol (methanol 1.5% to 2.5% gradient).
 25 The fractions containing the more polar product were collected and evaporated to give Object Compound A (0.93 g).
 IR (CH_2Cl_2) : 1740, 1640 cm^{-1}
 NMR (DMSO- d_6 , δ) : 1.39 (9H, s), 1.43 (9H, s), 1.8-2.0 (1H, m), 2.1-2.3 (1H, m), 2.71 and 2.78 (3H, s), 2.8-3.1 (2H, m), 3.8-4.0 (2H, m), 3.87 (2H, s), 4.18 (1H, m), 4.42 (2H, s), 4.88 (1H, t, J = 7.5Hz), 4.9-5.1 (2H, m), 5.1 (2H, s), 7.0-7.3 (11H, m), 7.42 (1H, d, J = 7.7Hz), 7.93 (1H, br s), 8.08 (1H, d, J = 7.4Hz), 8.48 (1H, m)
 30 The fractions containing the less polar product were collected and evaporated to give Object Compound B (4.46 g).
 IR (CH_2Cl_2) : 3800, 3400, 1740, 1670, 1640 cm^{-1}
 NMR (DMSO- d_6 , δ) : 1.43 (9H, s), 1.75-2.1 (2H, m), 2.70 and 2.78 (3H, s), 2.8-3.1 (2H, m), 3.8-3.7 and 3.8-4.0 (2H, m), 4.2-4.5 (3H, m), 4.85-4.8 (1H, m), 4.9-5.1 (2H, m), 5.1 (2H, s), 7.0-7.5 (13H, m), 7.9 (1H, br s), 8.1 (1H, d, J = 8Hz), 8.44 (1H, m)

Example 16

40 A solution of Starting Compound (3.56 g) and anisole (3.0 ml) in methylene chloride (25 ml) was treated with trifluoroacetic acid (18 ml) at room temperature for an hour. After concentration, the residue was dissolved in ethyl acetate and neutralized to pH 8 with sodium hydrogencarbonate solution. The aqueous layer was acidified with 4N-hydrochloric acid to pH 3 and extracted three times with ethyl acetate. The combined organic layer was washed with sodium chloride solution and dried over magnesium sulfate. After concentration, the residue was triturated in a mixed solvent of ethyl acetate and IPE and the resulting powder was filtered, washed with diisopropyl ether and dried to give Object Compound (3.04 g).
 IR (Nujol) : 3300, 1730, 1620, 1530 cm^{-1}
 NMR (DMSO- d_6 , δ) : 1.75-2.1 (2H, m), 2.70 and 2.78 (3H, s), 2.8-3.2 (2H, m), 3.8-3.7 and 3.8-4.0 (2H, m), 4.31 (1H, br), 4.42 (2H, s), 4.9-5.1 (2H, m), 5.12 (2H, s), 7.0-7.3 (12H, m), 7.45 (1H, d, J = 7.7Hz), 7.93 (1H, s), 8.07 (1H, d, J = 7Hz), 8.44 (1H, m)

Example 17

55 To a solution of Starting Compound (900 mg) and HOBT (209 mg) in methylene chloride (20 ml) was added WSC \cdot HCl (295 mg) under ice-cooling. After stirring at the same temperature for twenty minutes, N,N-dimethylmethylenediamine (133 mg), and the solution was stirred overnight under cooling. After con-

centration, the residue was extracted with ethyl acetate (100 ml) with sodium hydrogen carbonate solution. The organic layer was washed with sodium chloride solution and dried over magnesium sulfate. After concentration, the residue was dissolved in THF (12 ml) and 4N-HCl/DOX (0.31 ml) was added. The mixture was stirred for half an hour and concentrated. The residue was triturated with diethyl ether, filtered, washed with diethyl ether, and dried to give Object Compound (0.87 g).

IR (Nujol) : 3250, 2700, 1680 (sh), 1640, 1530 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.7-2.1 (2H, m), 2.7-2.8 (9H, m), 2.8-3.1 (2H, m), 3.2 (2H, m), 3.45 (2H, m), 3.6-3.7 and 3.8-4.0 (2H, m), 4.3-4.5 (3H, m), 4.7 (1H, m), 4.9-5.1 (2H, m), 5.04 (2H, s), 8.95-7.3 (12H, m), 7.51 (1H, d, J = 7.7Hz), 7.98 (1H, s), 8.08 (1H, d, J = 7.4Hz), 8.47 (1H, m), 8.68 (1H, m), 10.58 (1H, br s)

10

Example 18

15 The object compound was obtained according to a similar manner to that of Example 15.

NMR (DMSO- d_6 , δ) : 1.75-2.2 (2H, m), 2.20 (8H, s), 2.8-2.8 (5H, m), 3.4 (2H, m), 3.6-3.7 (1H, m), 3.9 (1H, br), 4.2-4.4 (5H, m), 4.71 (1H, m), 4.9-5.05 (2H, m), 7.0-7.3 (12H, m), 7.54 (1H, d, J = 8Hz), 7.91 (1H, s), 8.0-8.05 (1H, m), 8.48 (1H, m)

20

Example 19

To a solution of Starting Compound (1.38 g) in methylene chloride (14 ml) was added TEA (0.74 ml) under ice-cooling. To this solution was added a solution of MsCl (0.21 ml) in methylene chloride (1 ml)

25 maintaining the temperature below 6 °C. After stirring for one hour, TEA (0.74 ml) was added and a solution of MsCl (0.21 ml) in methylene chloride (1 ml) was added dropwise. The mixture was stirred for additional half an hour and washed with water. The organic layer was dried over magnesium sulfate, and evaporated. The residue was subjected to a silica gel column chromatography (60 g) and eluted with a mixture of chloroform and methanol (50:1-30:1). The main fractions were evaporated to give Object Compound (1.57 g).

30 IR (Nujol) : 3250, 1630, 1525, 1170 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.9-2.1 (1H, m), 2.3-2.5 (1H, m), 2.88 (s) and 2.78 (s)(3H), 2.8-3.1 (2H, m), 3.22 (3H, s), 4.0-4.3 (2H, m), 4.41 (2H, br s), 4.7-5.0 (2H, m), 5.33 (1H, br s), 6.9-7.3 (12H, m), 7.45 (1H, d, J = 7Hz), 7.87 (1H, br s), 8.00 (1H, d, J = 8Hz), 8.5-8.8 (1H, m), 11.72 (1H, s)

35

Example 20

To a solution of Starting Compound (1.8 g) in DMSO (9 ml), sodium azide (0.39 g) was added. The 40 solution was heated at 70 °C for 13.5 hours. After cooling, ethyl acetate (50 ml) was added and the solution was washed with water (three times) and brine. The organic layer was dried over magnesium sulfate and concentrated to give the concentrate of Intermediate Compound (ca. 20 ml). To the solution was added triphenylphosphine (0.78 g), then heated at 50 °C for 2 hours. After adding water (0.18 ml), the mixture was heated at 65 °C for 4.5 hours. The precipitates were filtered, subjected to a silica gel column chromatography (10 g) and eluted with chloroform-methanol (4:1). The main fractions were evaporated to give Object Compound (0.95 g).

IR (Nujol) : 3300, 1640, 1605 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.5-1.7 (1H, m), 1.78 (2H, br s), 2.2-2.4 (1H, m), 2.88 (s) and 2.73 (s)(3H), 2.7-3.1 (2H, m), 3.3-3.5 (2H, m), 3.8-4.0 (1H, m), 4.3-4.7 (3H, m), 4.8-5.1 (1H, m), 6.9-7.3 (11H, m), 7.43 (1H, d, J = 8Hz), 7.5-7.7 (1H, m), 7.81 (1H, s), 8.00 (1H, d, J = 8Hz), 8.4-8.7 (1H, m), 11.83 (1H, s)

Example 21

88 In ethanol, Starting Compound (0.30 g) was dissolved under heating. After ice-cooling, 4N-HCl/DOX (0.16 ml) was added and the solution was evaporated. The residue was pulverized with ether, filtered and dried to give Object Compound (0.31 g).

IR (Nujol) : 3200, 1625, 1520 cm^{-1}

NMR (DMSO-d₆, δ) : 1.8-2.2 (1H, m), 2.50 (1H, br s), 2.72 (3H, s), 2.7-3.2 (2H, m), 3.7-4.3 (3H, m), 4.3-4.6 (2H, m), 4.6-5.1 (2H, m), 6.9-7.6 (13H, m), 7.8-8.1 (2H, m), 8.4 (3H, br s), 8.85-9.15 (1H, m), 11.82 (1H, m)

5 Example 22

To a solution of Starting Compound (1.5 g) and pyridine (0.23 ml) in mixed solvent of methylene chloride (30 ml) and DMF (20 ml) was added dropwise a solution of ethyloxalyl chloride (0.32 ml) in methylene chloride (3 ml) under ice-cooling. The solution was stirred for four hours at the same 10 temperature, during which period ethyloxalyl chloride (64 μl) and pyridine (48 μl) were added. After concentration, the product was extracted with ethyl acetate and the organic layer was washed successively with 1N hydrochloric acid, water, 5% sodium hydrogencarbonate solution, water, and sodium chloride solution and dried over magnesium sulfate. After concentration, the residue was applied to a column of 15 silica gel (60 g) eluting with a mixed solvent of chloroform and methanol (50:1) to give Object Compound (1.75 g) as an amorphous solid.

IR (Nujol) : 3260, 1750, 1690, 1640, 1525 cm⁻¹

NMR (DMSO-d₆, δ) : 1.22 (3H, t, J = 7Hz), 1.7-2.0 (1H, m), 2.3-2.8 (1H, m), 2.69 (s) and 2.78 (s) (3), 2.7-3.0 (1H, m), 3.0-3.2 (1H, m), 3.8-3.8 (1H, m), 4.0-4.8 (4H, m), 4.18 (2H, q, J = 7Hz), 4.8-4.8 (1H, m), 4.8-5.1 (1H, m), 6.9-7.3 (12H, m), 7.45 (1H, d, J = 7Hz), 7.85 (1H, s), 8.05 (1H, d, J = 8Hz), 8.6-8.8 (1H, m), 9.1-9.3 (1H, m), 11.89 (1H, s)

Example 23

25 The object compound was obtained according to a similar manner to that of Example 4.

mp : 125-130 °C

IR (Nujol) : 3490, 3320, 3180, 1720, 1695, 1605 cm⁻¹

NMR (DMSO-d₆, δ) : 1.9-2.4 (2H, m), 2.60, 2.72 and 2.78 (3H, s), 2.9-3.1 (2H, m), 3.75-3.9 (1H, m), 4.17-4.28 (1H, m), 4.3-4.5 (2H, m), 4.7-4.8 (1H, m), 4.9-5.2 and 5.4 (2H, m), 6.80 (2H, br), 6.8-7.7 (13H, m) 8.17 (1H, d, J = 8Hz), 8.5-8.7 (1H, m), 13.6 (1H, br)

Example 24

35 The object compound was obtained according to a similar manner to that of Example 21.

IR (Nujol) : 3250, 2850, 1630, 1530 cm⁻¹

NMR (DMSO-d₆, δ) : 1.75-2.1 (2H, m), 2.7-3.1 (11H, m), 3.5 (2H, m), 3.8-3.7 and 3.8-4.0 (2H, m), 4.3-4.5 (3H, m), 4.85-5.0 (5H, m), 7.0-7.3 (12H, m), 7.73 (1H, d, J = 7.9Hz), 8.0-8.15 (2H, m), 8.47 (1H, m), 11.28 (1H, br s)

40

Example 25

45 The object compounds were obtained according to a similar manner to that of the latter half of Example 1.

(1) NMR (DMSO-d₆, δ) : 1.85-2.05 (1H, m), 2.15-2.35 (1H, m), 2.7 and 2.77 (3H, s), 2.8-3.1 (2H, m), 3.83 (1H, d, J = 11.4Hz), 4.1 (1H, m), 4.42 (2H, s), 4.60-4.8 (1H, m), 4.9-5.1 (2H, m), 6.8 (2H, br), 7.0-7.3 (11H, m), 7.46 (1H, d, J = 3.7Hz), 7.87 (1H, br s), 8.03 (1H, d, J = 7.1Hz), 8.5 (1H, m), 11.7 (1H, s)

(2) IR (Nujol) : 3250, 1750, 1630, 1530 cm⁻¹

50 NMR (DMSO-d₆, δ) : 1.16 (3H, t, J = 7Hz), 1.8-1.9 (1H, m), 2.15-2.3 (1H, m), 2.69 and 2.77 (3H, s), 2.8-3.1 (2H, m), 3.8-4.2 (7H, m), 4.41 (2H, br s), 4.88 (1H, m), 4.98 (1H, m), 6.85-7.3 (11H, m), 7.49 (1H, d, J = 8.2Hz), 7.87 (1H, br s), 8.03 (1H, d, J = 7.2Hz), 8.44 (1H, m), 11.87 (1H, br s)

55 Example 26

The object compound was obtained according to a similar manner to that of the latter half of Example 1.

IR (Nujol) : 3200-3400, 2800, 1680-1600, 1550-1530 cm⁻¹

NMR (DMSO-d₆, δ) : 1.7-2.2 (2H, m), 2.7-3.1 (5H, m), 3.56-3.9 (2H, m), 4.3-4.6 (4H, m), 4.9-5.1 (2H, m), 7.0-7.3 (11H, m), 7.4-7.85 (1H, m), 7.9-8.1 (1H, m), 8.50 and 8.66 (1H, d, J = 8Hz), 8.8-8.9 (1H, m), 9.0-9.3 (1H, m)

5

Example 27

10 A solution of Starting Compound (703 mg) in a mixed solvent of ethanol (20 ml) and THF (5 ml) was hydrogenated under atmospheric pressure in the presence of 10% palladium on carbon (200 mg) at room temperature for two hours. Filtration and concentration gave Object Compound (500 mg) as an amorphous solid.

IR (Nujol) : 3250, 1710, 1630, 1540 cm⁻¹

NMR (DMSO-d₆, δ) : 2.72 and 2.79 (3H, s), 2.4-3.0 (4H, m), 4.43 (2H, m), 4.7-5.2 (2H, m), 6.9-7.3 (13H, m), 7.55 (1H, d, J = 8Hz), 7.63 (1H, d, J = 8Hz), 8.2 (1H, m), 8.6 (1H, m), 12.71 (1H, s)

15

Example 28

20 To an ice-cooled solution of Starting Compound (2.54 g), HCl¹-H-Gln-NHBu¹ (1.52 g), and HOBT (0.648 g) in DMF (40 ml), was added WSC (0.783 g). After stirring at the same temperature for two hours and at room temperature for half an hour, NMM (0.18 ml) was added and the solution was stirred overnight. The solution was concentrated and the residue was triturated with water under cooling. Filtration and recrystallization of the precipitates gave Object Compound (1.42 g).

mp : 205-208 °C

25 IR (Nujol) : 3300, 1680 (sh), 1642, 1630, 1545, 1535 cm⁻¹

NMR (DMSO-d₆, δ) : 1.24 (9H, s), 1.8-2.2 (4H, m), 2.5-3.1 (4H, m), 2.71 and 2.78 (3H, s), 4.0-4.6 (3H, m), 4.7-5.1 (2H, m), 6.9-7.3 (13H, m), 7.38 (2H, s), 7.44 (1H, d, J = 8Hz), 7.82 (1H, d, J = 8Hz), 7.9 (1H, m), 8.2 (1H, m), 8.5 (1H, m), 11.54 (1H, s)

30

Elemental Analysis. Calculated for C ₃₅ H ₄₇ N ₇ O ₆ · H ₂ O :	
Found :	C 64.40, H 6.79, N 13.47 C 64.81, H 6.50, N 13.62

35

Example 29

40 To an ice-cooled solution of Starting Compound (3.02 g) and BSA (2.27 g) in methylene chloride (50 ml) was added indole-3-carbonyl chloride (1.0 g). The solution was stirred at this temperature for two hours and BSA (0.82 g) and indole-3-carbonyl chloride (0.2 g) was added. The solution was washed with water, diluted sodium hydrogencarbonate solution 0.5N hydrochloric acid and sodium chloride solution and dried over magnesium sulfate. After concentration, the residue was applied to a silica gel (50 g) column and eluted firstly with chloroform and secondly with chloroform-methanol (100:1 to 100:2.5 gradient elution) to give Object Compound (3.3 g) as an amorphous solid.

IR (Nujol) : 3270, 1740, 1635 (sh), 1620, 1550, 1540 cm⁻¹

45 NMR (DMSO-d₆, δ) : 2.84 and 2.81 (3H, s), 2.8-3.3 (4H, m), 4.27 and 4.87 (2H, ABq, J = 15Hz), 5.0-5.3 (2H, m), 5.13 (2H, s), 7.03 (5H, s), 7.0-7.7 (13H, m), 7.8-8.1 (2H, m), 8.67 (1H, s)

55

Example 30

55 A solution of Starting Compound (2.87 g) in ethanol (80 ml) was added 10% palladium on carbon (780 mg). The solution was hydrogenated at room temperature for two hours under atmospheric pressure. After filtration, 4N-HCl/DOX (1.1 ml) was added to the filtrate and the solution was concentrated. Water (100 ml) and ethyl acetate (50 ml) were added to the residue and the aqueous layer was lyophilized to give Object

Compound (2.09 g) as an amorphous solid.

IR (Nujol) : 3400-3100, 2750-2600, 1630, 1535 cm^{-1}

NMR (DMSO-d₆, δ) : 1.2-1.9 (8H, m), 2.70 and 2.77 (3H, s), 2.6-3.1 (4H, m), 4.2-4.6 (3H, m), 4.9-5.2 (1H, m), 6.9-7.5 (14H, m), 7.8-8.4 (6H, m)

5

10

Elemental Analysis. Calculated for $\text{C}_{32}\text{H}_{37}\text{N}_5\text{O}_3 \cdot \text{HCl}$:	
Found :	C 66.71, H 6.65, N 12.18, Cl 6.15 C 62.22, H 6.33, N 11.63, Cl 7.51

15

Example 31

To an ice-cooled solution of Starting Compound (1.0 g), 3-diethylaminopropionic acid hydrochloride (318 mg), and HOBT (283 mg) was added WSC (271 mg). The solution was stirred at the same temperature for an hour and at room temperature for six hours. During these reaction period, NMM (0.1 ml) and WSC·HCl (33 mg) were added. The solution was concentrated and was acidified with diluted hydrochloric acid to pH 2 and washed twice with ethyl acetate. The aqueous layer was neutralized to pH 8 with sodium hydrogencarbonate solution and extracted twice with ethyl acetate. The organic layer was dried with magnesium sulfate and concentrated. The residue was dissolved in THF (15 ml) and 4N-HCl/DOX (0.35 ml) was added. After evaporation of THF, the residue was dissolved in water and washed with diethyl ether. The aqueous layer was lyophilized to give Object Compound (803 mg).

IR (Nujol) : 3200, 1630, 1535 cm^{-1}
NMR (DMSO-d₆, δ) : 1.17 (8H, s), 1.2-1.9 (8H, m), 2.5-2.7 (2H, m), 2.73 and 2.8 (3H, s), 2.9-3.4 (10H, m), 4.4-4.7 (3H, m), 4.8-5.1 (1H, m), 7.0-7.3 (12H, m), 7.4 (1H, m), 8.1-8.4 (3H, m), 10.3 (1H, br), 11.7 (1H, s)

30

Example 32

Starting Compound (0.82 g) and anisole (1.0 ml) was dissolved in methylene chloride (5 ml), and under ice-cooling, TFA (15 ml) was added to the solution. The solution was stirred at the same temperature for twelve minutes and at room temperature for twenty minutes. After evaporation of TFA, 4N-HCl/DOX (0.6 ml) was added to the residue. The mixture was concentrated again and the residue was triturated with IPE. The powder was filtered, washed with ether, and dried under vacuum to give the intermediate (0.68 g). This intermediate was dissolved in methylene chloride (10 ml), and TEA (197 mg) and AC₂O (99 mg) were added into the solution at -15 °C. After stirring the solution for half an hour, DMF (15 ml) and methanol (2 ml) was added to the solution to dissolve the precipitates and the solution was concentrated. The product was extracted with ethyl acetate and the organic layer was washed successively with water, diluted sodium hydrogencarbonate solution, 0.5N hydrochloric acid, and sodium chloride solution, and was dried over magnesium sulfate. After filtration, the precipitates formed after left standing were collected, washed with ethyl acetate, and dried to give Object Compound (0.36 g).

mp : 198-201 °C

IR (Nujol) : 3250, 1660 (sh), 1635, 1620, 1550, 1250, 1215 cm^{-1}
NMR (DMSO-d₆, δ) : 1.0 (3H, d, $J = 6\text{Hz}$), 1.2-1.8 (8H, m), 1.88 (3H, s), 2.70 and 2.77 (3H, s), 2.8-3.2 (4H, m), 3.8-4.2 (2H, m), 4.35-4.6 (3H, m), 4.70 (1H, d, $J = 5\text{Hz}$), 4.85-5.2 (1H, m), 6.9-7.3 (11H, m), 7.3-7.75 (5H, m), 8.0-8.35 (3H, m), 11.5 (1H, br)

50

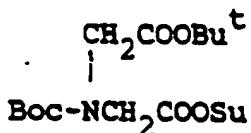
55

Elemental Analysis. Calculated for $\text{C}_{38}\text{H}_{45}\text{N}_5\text{O}_5 \cdot 1/2\text{CH}_3\text{COOC}_2\text{H}_5$:	
Found :	C 66.84, H 6.79, N 12.31 C 66.10, H 6.93, N 11.58

Example 33

To a solution of Starting Compound (0.70 g) in DMF (10 ml), NMM (0.14 ml) was added at 4 °C. Then

5



10

(0.47 g) was added and stirred at room temperature for 2 hours. After evaporation, the residue was dissolved in methylene chloride (20 ml) and N,N'-dimethyl-1,3-propanediamine (10 drops) was added. The mixture was stirred for 30 minutes, then evaporated. The residue was dissolved ethyl acetate, and the organic layer was washed successively with 2% hydrochloric acid, water, 5% sodium hydrogencarbonate, water and brine. The organic layer was dried over anhydrous magnesium sulfate, then evaporated. The residue was subjected to column chromatography on silica gel (30 g) and eluted with a mixture of chloroform and methanol (20:1). The fractions containing the object compound were combined and evaporated. The residue was pulverized with IPE, filtered and dried to give Object Compound (0.87 g).

15 IR (Nujol) : 3280, 1730, 1710, 1630, 1620, 1545 cm^{-1}
 NMR (DMSO- d_6 , δ) : 1.20-1.50 (4H, m), 1.33 (s) and 1.35 (s)(8H), 1.40 (s) and 1.41 (s)(8H), 1.50-1.80 (2H, m), 2.72 (s) and 2.81 (s)(3H), 2.80-3.20 (4H, m), 3.70-3.90 (4H, m), 4.30-4.60 (3H, m), 4.80-5.10 (1H, m), 7.00-7.40 (12H, m), 7.40-7.50 (1H, m), 7.70-7.85 (1H, m), 7.90-8.00 (1H, m), 8.10-8.20 (2H, m), 8.30-8.40 (1H, m), 11.80 (1H, s)

20

25

Example 34

To a solution of Starting Compound (0.70 g) and morpholinecarbonyl chloride (0.18 g) in DMF (10 ml), NMM (0.28 ml) was added. The mixture was stirred for 4 hours and allowed to stand overnight. The evaporated residue was dissolved in a mixture ethyl acetate and THF and washed successively with 2% hydrochloric acid, water, 5% sodium hydrogencarbonate, water and brine. The organic layer was dried over anhydrous magnesium sulfate and evaporated. The residue was subjected to column chromatography on silica gel (25 g) and eluted with a mixture of chloroform and methanol (20:1). The fractions containing the object compound were combined and evaporated to give Object Compound (0.29 g).

25 IR (Nujol) : 3270, 1630, 1540 cm^{-1}
 NMR (DMSO- d_6 , δ) : 1.20-1.55 (4H, m), 1.55-1.80 (2H, m), 2.72 (s) and 2.80 (s)(3H), 2.80-3.10 (4H, m), 3.10-3.30 (4H, m), 3.40-3.80 (4H, m), 4.30-4.60 (3H, m), 4.80-5.10 (1H, m), 6.40-6.55 (1H, m), 7.00-7.40 (12H, m), 7.40-7.50 (1H, m), 7.77 (1H, d, J =8Hz), 8.10-8.20 (2H, m), 8.37 (1H, d, J =8Hz), 11.80 (1H, s)

30

35

Example 35

To an ice-cooled solution of Starting Compound (1.0 g) in DMF (10 ml) were added pyridine (1.5 ml) and acetic anhydride (0.7 ml). The solution was stirred three hours at room temperature and DMAP (0.1 g) was added. The solution was stirred for further an hour and concentrated. The product was extracted with ethyl acetate and the organic layer was washed successively with 1N-hydrochloric acid, water, 5% sodium hydrogencarbonate solution, water, and sodium chloride solution and dried over magnesium sulfate. Evaporation and trituration of the extract gave Object Compound (0.85 g) as an amorphous solid.

35 mp : 89-91 °C
 IR (Nujol) : 3330, 1740, 1635, 1605, 1245 cm^{-1}
 NMR (DMSO- d_6 , δ) : 1.8-2.3 (2H, m), 1.98 (3H, s), 2.89 (s) and 2.78 (s)(3H), 2.7-3.1 (2H, m), 3.8-4.3 (2H, m), 3.85 (3H, s), 4.41 (2H, s), 4.7-4.8 (1H, m), 4.8-5.1 (1H, m), 5.24 (1H, br s), 6.9-7.4 (12H, m), 7.50 (1H, d, J =8Hz), 7.91 (1H, br s), 8.08 (1H, d, J =8Hz), 8.52 (1H, br s)

40

45

5

Elemental Analysis. Calculated for C ₃₄ H ₃₆ N ₄ O ₅ • 1/2H ₂ O	
Found :	C 69.25, H 6.32, N 9.50
	C 69.84, H 6.28, N 9.52

10 Example 36

To an ice-cooled solution of Starting Compound (1.0 g), Z-Gly-OH (0.4 g), and HOBT (0.26 g) in DMF (10 ml) was added WSC-HCl (0.37 g). The solution was stirred at room temperature for three hours and concentrated. The product was extracted with ethyl acetate and the organic layer was successively washed with water, 1N-hydrochloric acid, water, 5% sodium hydrogencarbonate solution, water, and sodium chloride solution and dried over magnesium sulfate. After evaporation, the crude product was purified on a silica gel column (75 g) eluting with chloroform-methanol (20:1) to give Object Compound (1.3 g) as an amorphous solid.

IR (Nujol) : 3250, 1720, 1710, 1680, 1635, 1525 cm⁻¹

NMR (DMSO-d₆, δ) : 1.8-1.9 (1H, m), 2.3-2.8 (1H, m), 2.88 (s) and 2.73 (s)(3H), 2.7-3.2 (2H, m), 3.4-3.7 (3H, m), 4.0-5.0 (8H, m), 5.02 (2H, s), 6.9-7.5 (10H, m), 7.81 (1H, s), 8.01 (1H, d, J=8Hz), 8.1-8.3 (1H, m), 8.5-8.7 (1H, m), 11.88 (1H, s)

25 Example 37

To a solution of Starting Compound (0.93 g) in ethanol (25 ml) was added 4N-HCl/DOX (3.25 ml) and the solution was hydrogenated under atmospheric pressure in the presence of 10% palladium on carbon (1.3 g) for ten hours. After filtration and evaporation, the residue was dissolved in water (50 ml) and the solution was shaken twice with ethyl acetate (25 ml). The aqueous layer was separated and filtered through a Millipore filter and lyophilized to give Object Compound (0.49 g) as a powder.

IR (Nujol) : 3220, 1625, 1525 cm⁻¹

NMR (DMSO-d₆, δ) : 1.7-2.0 (1H, m), 2.4-2.8 (1H, m), 2.88 (s) and 2.74 (s)(3H), 2.7-3.2 (2H, m), 3.4-3.9 (3H, m), 4.1-5.1 (8H, m), 6.9-7.4 (12H, m), 7.45 (1H, d, J=7Hz), 7.79 (1H, s), 7.98 (1H, d, J=8Hz), 8.20 (3H, br s), 8.4-8.7 (1H, m), 8.7-8.9 (1H, m), 11.84 (1H, s)

Example 38

Starting Compound (1.13 g) was dissolved in ethanol (200 ml), and the solution was hydrogenated under atmospheric pressure in the presence of 20% palladium hydroxide on carbon (2.2 g) for three hours. After filtration and evaporation, the residue was triturated with IPE, and dried to give Object Compound (0.53 g) as an amorphous solid.

IR (Nujol) : 3250, 1630, 1525 cm⁻¹

NMR (DMSO-d₆/D₂O, δ) : 1.8-1.9 (1H, m) 1.9-2.1 (2H, m), 2.2-2.5 (3H, m), 2.89 (s) and 2.75 (s)(3H), 2.7-3.2 (2H, m), 3.78 (1H, t, J=6Hz), 4.0-4.8 (5H, m), 4.8-5.1 (1H, m), 6.9-7.3 (12H, m), 7.47 (1H, d, J=7Hz), 7.81 (1H, s), 7.99 (1H, d, J=8Hz)

50 Example 39

To an ice-cooled solution of Starting Compound (1.0 g) and TEA (0.27 ml) in DMF (10 ml) was added succinic anhydride (0.18 g) at a time. The solution was stirred at the same temperature for three quarters an hour and concentrated. The product was extracted with ethyl acetate and the organic layer was washed successively with 1N hydrochloric acid, water and 5% sodium hydrogencarbonate solution. The last aqueous layer was then acidified to pH 2 with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed sodium chloride solution and dried with magnesium sulfate. After concentration the residue (1.1 g) was dissolved in a mixed solvent of ethanol (70 ml) and water (130 ml) and 1N sodium

hydroxide solution (1.55 ml) was added. After evaporation of the alcohol, the solution was filtered through a Millipore Filter (trademark, prepared by Millipore Corporation) (type HA, 0.45 μ m) and lyophilized to give Object Compound (1.07 g) as a powder.

IR (Nujol) : 3200, 1640, 1630, 1570-1515 cm^{-1}

5 NMR (DMSO-d₆, δ) : 1.8-1.9 (1H, m), 2.1-2.3 (4H, m), 2.3-2.5 (1H, m), 2.68 (s) and 2.74 (s)(3H), 2.7-3.2 (2H, m), 4.0-4.8 (5H, m), 4.8-5.1 (1H, m), 6.9-7.4 (12H, m), 7.47 (1H, d, J =7Hz), 7.82 (1H, s), 8.00 (1H, d, J =8Hz), 8.5-8.8 (2H, m), 12.17 (1H, broad)

10 Example 40

To an ice-cooled solution of Starting Compound (1.45 g) in ethanol (30 ml) was added a solution of 1N sodium hydroxide (1.94 ml). The solution was stirred at room temperature for two hours. After evaporation of alcohol, water (50 ml) was added and the solution was lyophilized to give Object Compound (1.26 g) as a powder.

15 IR (Nujol) : 3300 (broad), 1635, 1520 cm^{-1}

NMR (DMSO-d₆, δ) : 1.7-1.9 (1H, m), 2.3-2.5 (1H, m), 2.67 (s) and 2.75 (s)(3H), 2.7-3.0 (1H, m), 3.0-3.2 (1H, m), 3.6-3.8 (1H, m), 4.0-4.8 (5H, m), 4.8-5.1 (1H, m), 6.9-7.3 (12H, m), 7.48 (1H, d, J =7Hz), 7.84 (1H, s), 8.03 (1H, d, J =8Hz), 8.4-8.7 (2H, m), 11.85 (1H, broad)

20

Example 41

Starting Compound (1.0 g) was dissolved in THF (15 ml). Sodium 2-ethylhexanoate (287 mg) was added to the solution. THF (25 ml) was added into it, and the suspended mixture was stirred for half an hour. After concentration of the solution to one-fourth of its original volume, diethyl ether (50 ml) was added and the resulting precipitated were collected. After drying, the product was dissolved in water (100 ml) and shaken once with diethyl ether (50 ml). The aqueous layer was lyophilized to give Object Compound (820 mg) as a powder.

25 IR (Nujol) : 3350, 1630-1600 cm^{-1}

NMR (DMSO-d₆, δ) : 1.75-2.1 (2H, m), 2.69 and 2.78 (3H, s), 2.8-3.1 (2H, m), 3.6-3.74 and 3.8-4.0 (2H, m), 4.30 (1H, m), 4.41 (2H, s), 4.54 (2H, s), 4.72 (1H, m), 4.8-5.2 (2H, m), 6.85-7.4 (13H, m), 7.83 (1H, s), 8.03 (1H, d, J =7Hz), 8.44 (1H, m)

30

Example 42

To a solution of Starting Compound (1.0 g) in DMF (5 ml), was added methyl mercaptan sodium salt (ca. 15% in water, 1.35 ml). The solution was stirred at room temperature for 8 hours and allowed to stand overnight. Then the solution was poured to a mixture of ethyl acetate and sodium hydrogencarbonate solution. The organic layer was washed with sodium hydrogencarbonate solution, 1N sodium hydroxide solution, water and brine, and was dried over magnesium sulfate. After evaporation, the crude product was purified by column chromatography on silica gel (40 g) eluting with chloroform-methanol (50:1) crystallization with ethanol-hexane gave Object Compound (0.48 g).

35 IR (Nujol) : 3360, 1705, 1640, 1620, 1605, 1530 cm^{-1}

NMR (DMSO-d₆, δ) : 1.4-2.0 (2H, m), 2.11 (3H, s), 2.4-3.7 (3H, m), 2.68 (s), 2.78 (s) and 2.80 (s)(3H), 3.83 (s) and 3.88 (s)(3H), 4.0-5.2 (6H, m), 6.9-7.4 (12H, m), 7.50 (1H, d, J =8Hz), 7.95 (1H, br s), 8.02 (1H, d, J =8Hz), 8.44 (1H, m)

40

Example 43

The object compounds were obtained according to a similar manners to those of Preparation 4 and Example 4, successively.

45 (1) IR (Nujol) : 3310, 1655, 1650, 1620, 1565, 1545 cm^{-1}

NMR (DMSO-d₆, δ) : 1.8-2.1 (2H, m), 2.03 (3H, s), 2.4-2.6 (2H, m), 2.72 (s) and 2.81 (s)(3H), 2.8-3.1 (2H, m), 3.85 (3H, s), 4.3-4.7 (3H, m), 4.9-5.1 (1H, m), 7.0-7.3 (12H, m), 7.50 (1H, d, J =7Hz), 7.85 (1H, d, J =8Hz), 8.1-8.2 (1H, m), 8.12 (1H, s), 8.3-8.5 (1H, m)

(2) mp : 85-87 °C

IR (Nujol) : 3300, 1630, 1535 cm⁻¹NMR (DMSO-d₆, δ) : 1.04 (d, J = 6Hz) and 1.08 (d, J = 6Hz)(3H), 2.71 (s) and 2.80 (s)(3H), 2.8-3.1 (2H, m), 3.88 (3H, s), 4.0-4.1 (1H, m), 4.3-4.6 (3H, m), 4.92 (1H, d, J = 6Hz), 4.9-5.1 (1H, m), 6.9-7.3 (12H, m), 7.43 (1H, d, J = 8Hz), 7.52 (1H, d, J = 8Hz), 8.09 (1H, d, J = 8Hz), 8.13 (1H, s), 8.34 (1H, d, J = 8Hz)

6

10

Elemental Analysis. Calculated for
C₃₁H₃₄N₄O₆ • 1/2H₂OC 69.51, H 6.59, N 10.46
Found : C 69.73, H 6.44, N 10.38

18

(3) IR (Nujol) : 3300, 1630, 1540, 1240 cm⁻¹NMR (DMSO-d₆, δ) : 1.23 (d, J = 7Hz) and 1.28 (d, J = 7Hz)(3H), 2.73 (s) and 2.81 (s)(3H), 2.8-3.1 (2H, m), 3.84 (3H, s), 4.4-4.8 (3H, m), 4.9-5.1 (1H, m), 7.0-7.3 (13H, m), 7.50 (1H, d, J = 8Hz), 7.80 (d, J = 8Hz) and 7.83 (d, J = 8Hz)(1H), 8.11 (1H, s), 8.12 (1H, d, J = 8Hz), 8.3-8.4 (1H, m)

(4) mp : 89-91 °C

20

IR (Nujol) : 3260, 1670, 1630, 1585, 1570, 1530, 1100 cm⁻¹NMR (DMSO-d₆, δ) : 1.7-2.0 (1H, m), 2.0-2.3 (1H, m), 2.69 (s) and 2.77 (s)(3H), 2.7-3.1 (2H, m), 3.19 (3H, s), 3.7-4.1 (8H, m), 4.3-4.5 (2H, m), 4.5-4.7 (1H, m), 4.8-5.1 (1H, m), 6.9-7.3 (12H, m), 7.49 (1H, d, J = 8Hz), 7.91 (1H, br s), 8.05 (1H, d, J = 8Hz), 8.44 (1H, br s)

28

Elemental Analysis. Calculated for
C₃₃H₃₆N₄O₆ • 1/2H₂OC 70.57, H 6.64, N 9.97
Found : C 70.76, H 6.78, N 9.77

30

(5) IR (Neat) : 1640-1630, 1540 cm⁻¹NMR (DMSO-d₆, δ) : 2.8-3.4 (9H, m), 3.5-3.7 (1H, m), 3.7-3.9 (3H, m), 4.0-4.8 (4H, m), 5.0-5.3 (1H, m), 5.5-5.7 (1H, m), 6.8-7.4 (17H, m), 7.4-7.8 (1H, m), 7.8-8.2 (3H, m)

38

Example 44

The object compounds were obtained according to a similar manner to that of Example 4.

40

(1) IR (Nujol) : 3260, 1735, 1645 (sh), 1630, 1545 cm⁻¹NMR (DMSO-d₆, δ) : 2.8-3.1 (4H, m), 2.79 (3H, s), 4.40 (2H, s), 4.8-5.1 (2H, m), 5.05 (2H, s), 6.9-7.8 (19H, m), 8.3 (1H, m), 8.65 (1H, m), 11.8 (1H, s)

(2) mp : 222-224 °C

IR (Nujol) : 3260, 1680 (sh), 1680 (sh), 1645, 1630, 1550, 1535 cm⁻¹

45

NMR (DMSO-d₆, δ) : 1.23 (9H, s), 1.8-2.7 (4H, m), 2.55-3.05 (4H, m), 2.70 and 2.78 (3H, s), 4.0-4.3 (1H, m), 4.3-4.7 (2H, m), 4.7-5.1 (2H, m), 6.84 (1H, br s), 6.9-7.3 (14H, m), 7.3-7.7 (3H, m), 7.8-8.1 (1H, m), 8.2-8.4 (1H, m), 8.45-8.85 (1H, m), 11.58 (1H, s)(3) NMR (CDCl₃, δ) : 2.58 and 2.81 (3H, s), 2.5-3.1 (4H, m), 3.73 and 3.75 (2H, s), 4.07 and 4.19 (ABq, J = 18.5Hz) and 4.25 and 4.63 (ABq, J = 14.6Hz) (Two set of ABq, 2H), 4.8-5.1 (4H, m), 6.7-7.4 (16H, m), 7.5-7.8 (1H, m), 8.49 (1H, s)

50

(4) IR (Nujol) : 3260, 1710, 1620, 1550, 1530, 1240 cm⁻¹NMR (DMSO-d₆, δ) : 1.2-2.8 (8H, m), 2.69 and 2.73 (3H, s), 2.8-3.15 (4H, m), 4.3-4.7 (3H, m), 4.8-5.1 (1H, m), 5.08 (2H, s), 6.9-7.7 (18H, m), 8.2-8.5 (2H, m), 11.58 (1H, s)(5) IR (Nujol) : 3300, 1700, 1640, 1630 cm⁻¹

55

NMR (DMSO-d₆, δ) : 1.0-1.7 (8H, m), 2.71 (s) and 2.78 (s)(3H), 2.8-3.1 (4H, m), 3.4-3.7 (2H, m), 4.2-4.4 (1H, m), 4.43 (2H, s), 4.8-5.1 (1H, m), 5.00 (2H, s), 6.8-7.5 (20H, m), 7.55 (1H, d, J = 8Hz), 7.92 (1H, d, J = 8Hz), 8.40 (1H, d, J = 8Hz), 10.88 (1H, s)(6) IR (Nujol) : 3250, 1630, 1490 cm⁻¹

NMR (DMSO-d₆, δ) : 1.7-2.0 and 2.1-2.3 (2H, m), 2.7-3.1 (5H, m), 3.4-4.0 (4H, m), 4.2-4.75 (4H, m), 4.85-5.2 (2H, m), 6.8-7.35 (11H, m), 7.5 (1H, m), 7.87 and 7.8 (1H, m), 8.42 (d, J=8.1Hz) and 8.9 (m)(1H), 12.95 and 12.98 (1H, br s)

(7) IR (CH₂Cl₂) : 3600, 3400, 3300, 1620, 1505 cm⁻¹

5 NMR (DMSO-d₆, δ) : 1.7-2.4 (2H, m), 2.6-3.1 (9H, m), 3.25-3.45 (2H, m), 4.1-4.6 (4H, m), 4.85-5.1 (2H, m), 6.8-6.7 (2H, m), 6.9-7.4 (12H, m), 8.3-8.4 (m) and 8.7-8.8 (m)(1H), 9.1-9.15 (1H, m)

(8) IR (CH₂Cl₂) : 1650 (sh), 1630, 1600, 1480, 1380, 1150 cm⁻¹

NMR (DMSO-d₆, δ) : 1.42 and 1.53 (9H, s), 1.8-2.05 (2H, m), 2.64 and 2.69 (3H, s), 2.75-3.1 (4H, m), 3.4-3.6 (2H, m), 4.3-4.8 (4H, m), 4.8-5.2 (3H, m), 6.85-7.0 (3H, m), 7.1-7.4 (10H, m), 7.73 (1H, d, J=8Hz), 8.40 (1H, d, J=8Hz)

10 (9) mp : 122-124 °C

NMR (DMSO-d₆, δ) : 1.7-2.1 (2H, m), 2.69 and 2.77 (3H, s), 2.9-3.1 (2H, m), 3.6-3.7 (1H, m), 3.85 (1H, m), 3.85 (3H, s), 4.2-4.8 (3H, m), 4.65-4.75 (1H, m), 4.9-5.05 (2H, m), 7.0-7.3 (12H, m), 7.49 (1H, d, J=7.9Hz), 7.88 (1H, s), 8.08 (1H, d, J=7.5Hz), 8.4 (1H, m)

15 (10) mp : 92-98 °C

IR (Nujol) : 3430, 3300, 1680, 1630, 1605, 1545 cm⁻¹

NMR (DMSO-d₆, δ) : 1.51 (6H, s), 1.7-2.1 (2H, m), 2.69 and 2.77 (3H, s), 2.8-3.2 (2H, m), 3.67 (br s) and 3.9-4.1 (m)(1H), 4.2-4.5 (3H, m), 4.8-5.0 (4H, m) 6.9-7.3 (12H, m), 7.58 (1H, d, J=7.8Hz), 7.89 (1H, m), 8.64 (1H, d, J=7.3Hz), 8.45 (1H, m)

20 (11) IR (Nujol) : 3250, 1840, 1600, 1525, 1510 cm⁻¹

NMR (DMSO-d₆, δ) : 1.8-2.3 (2H, m), 2.72 and 2.79 (3H, s), 2.91 (1H, d of ABq, J=13.9Hz, 6.3Hz), 3.06 (1H, d of ABq, J=13.9Hz, 7.4Hz), 3.6-4.1 (2H, m), 4.3-4.53 (3H, m), 4.8-4.7 (1H, m), 4.9-5.2 (2H, m), 6.9-7.5 (13H, m), 7.7 (1H, m), 8.5-8.8 (1H, m), 11.89 and 11.79 (1H, s)

(12) IR (Nujol) : 3280, 1842, 1608, 1580, 1510 cm⁻¹

25 NMR (DMSO-d₆, δ) : 1.7-2.2 (2H, m), 2.6-3.1 (5H, m), 3.5-3.8 (2H, m), 4.2-4.6 (4H, m), 4.9-5.1 (2H, m), 6.4-7.8 (14H, m), 8.4 and 8.8 (1H, m), 8.87 (1H, br s)

(13) mp : 135-137 °C

IR (Nujol) : 3280, 1670, 1645, 1595, 1580, 1512 cm⁻¹

NMR (DMSO-d₆, δ) : 1.7-2.2 (2H, m), 2.6-3.1 (5H, m), 3.5-3.7 (2H, m), 3.80 (3H, s), 3.82 (3H, s), 4.2-4.6 (4H, m), 4.8-5.2 (2H, m), 6.8-7.5 (12H, m), 8.4 and 8.9 (1H, m), 8.82 (1H, br s)

30 (14) mp : 103-105 °C

IR (Nujol) : 3420, 3330, 1685, 1645, 1630, 1540 cm⁻¹

NMR (DMSO-d₆, δ) : 0.77 (d, J=8Hz) and 0.88 (d, J=8Hz)(8H), 1.2-2.3 (8H, m), 2.71 (s), 2.78 (s) and 2.87 (s)(3H), 2.8-3.1 (2H, m), 3.3-3.7 (2H, m), 4.1-4.6 (4H, m), 4.8-5.1 (2H, m), 7.0-7.4 (10H, m), 8.30 (d, J=8Hz) and 8.72 (d, J=8Hz)(1H)

Elemental Analysis. Calculated for C ₂₈ H ₃₇ N ₃ O ₄ :	
40 Found :	C 70.12, H 7.78, N 8.76 C 69.98, H 7.85, N 8.69

45 (15) IR (Nujol) : 3270, 1840 (sh), 1630, 1595, 1520, 1204 cm⁻¹

NMR (DMSO-d₆, δ) : 1.7-2.3 (2H, m), 2.79 and 2.86 (3H, s), 2.90 (1H, d, of ABq, J=13.9Hz, 6.5Hz), 3.06 (1H, d of ABq, J=13.9Hz, 7.5Hz), 3.77 (3H, s), 3.85-3.85 (1H, m), 3.9-4.1 (1H, m), 4.3-4.5 (3H, m), 4.6-4.7 (1H, m), 4.9-5.2 (2H, m), 6.8-7.4 (14H, m), 8.5-8.8 (1H, m), 11.34 and 11.43 (1H, s)

(16) IR (Nujol) : 3270, 1630, 1600, 1530 cm⁻¹

50 NMR (DMSO-d₆, δ) : 1.7-2.1 (2H, m), 2.38 (3H, s), 2.72 and 2.79 (3H, s), 2.91 (1H, d of ABq, J=13.4Hz and 7.1Hz), 3.08 (1H, d of ABq, J=13.4Hz, 7.4Hz), 3.7-4.1 (2H, m), 4.3-4.55 (3H, m), 4.8-4.75 (1H, m), 4.9-5.15 (2H, m), 6.8-7.4 (14H, m), 8.5-8.8 (1H, m), 11.34 and 11.45 (1H, s)

(17) IR (Nujol) : 3300, 1630, 1525 cm⁻¹

NMR (DMSO-d₆, δ) : 1.8-1.8 (1H, m), 2.0-2.2 (1H, m), 2.4-3.2 (5H, (singlet at 2.71 and 2.79), 3.6-3.72 (2H, m), 3.83 (3H, s), 4.2-5.2 (8H, m), 6.55-7.35 (13H, m), 7.4-7.7 (2H, m), 8.5-8.82 (1H, m)

55 (18) IR (Nujol) : 3220, 1840, 1530 cm⁻¹

NMR (DMSO-d₆, δ) : 1.8-2.3 (2H, m), 2.45-3.1 (5H, m), 3.7-4.1 (2H, m), 4.25-4.55 and 4.85-4.8 (5H, m), 4.9-5.1 and 5.4-5.5 (1H, m), 7.85-7.35 (10H, m), 7.8-8.2 (5H, m), 8.4-8.7 (1H, m)

(19) IR (CH₂Cl₂) : 3400, 1670, 1635 cm⁻¹

NMR (DMSO-d₆, δ) : 1.7-2.1 and 2.2-2.4 (2H, m), 2.68-3.1 (5H, m), 3.82 and 3.92 (3H, s), 3.35-3.6 (2H, m), 4.0-5.3 (8H, m), 6.55-7.55 (13H, m), 7.9-8.05 (2H, m), 8.36 (d, J = 7.8Hz) and 8.94 (m)(1H)
 (20) mp : 157-158 °C
 IR (Nujol) : 3420, 3300, 1625 cm⁻¹

5 NMR (DMSO-d₆, δ) : 2.72 (s) and 2.80 (s)(3H), 2.8-3.1 (2H, m), 3.6-3.7 (2H, m), 3.85 (3H, s), 4.3-4.6 (3H, m), 4.92 (1H, t, J = 5.5Hz), 4.8-5.1 (1H, m), 7.0-7.3 (12H, m), 7.51 (1H, d, J = 8Hz), 7.8-7.7 (1H, m), 8.1-8.2 (2H, m), 8.34 (1H, t, J = 8Hz)

10	Elemental Analysis. Calculated for C₃₀H₃₂N₄O₄ :	
	Found : C 70.29, H 6.29, N 10.93	C 70.19, H 6.28, N 10.92

15 (21) IR (Nujol) : 3300, 1620, 1512 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.7-2.4 (2H, m), 2.6-3.0 (5H, m), 3.6-4.1 (2H, m), 4.3-4.5 (3H, m), 4.8-4.7 (1H, m), 4.8-5.2 (2H, m), 6.8-7.8 (14H, m), 8.52 and 8.85 (d, J = 7.7Hz), 9.2 (1H, m)
 (20) mp : 124-128 °C
 IR (Nujol) : 3270, 1658, 1630 (sh), 1610, 1514 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.51 (8H, br s), 1.75-2.2 (2H, m), 2.6-3.0 (5H, m), 3.85 (1H, d, J = 9.8Hz), 3.9-4.1 (1H, m), 4.2-4.5 (3H, m), 4.8-5.0 (4H, m), 6.5-6.6 (2H, m), 6.8-7.4 (9H, m), 7.58 (1H, d, J = 7.8Hz), 7.9 (1H, br s), 8.04 (1H, d, J = 7.4Hz), 8.38 (1H, m), 9.22 (1H, s)
 (22) IR (Nujol) : 3280, 1630, 1510 cm⁻¹
 20 NMR (DMSO-d₆, δ) : 0.88 (8H, d, J = 8Hz), 1.2-2.3 (7H, m), 2.6-3.0 (5H, m), 3.3-3.5 (1H, m), 3.5-3.7 (1H, m), 4.1-4.8 (4H, m), 4.7-5.1 (2H, m), 6.8-6.7 (2H, m), 6.8-7.1 (4H, m), 7.2-7.3 (3H, m), 8.24 (d, J = 8Hz) and 8.85 (d, J = 8Hz)(1H), 9.20 (s) and 9.22 (s)(1H)
 (23) IR (Nujol) : 3280, 1630, 1510 cm⁻¹
 25 NMR (DMSO-d₆, δ) : 1.8-2.15 (2H, m), 2.87 and 2.75 (3H, s), 2.8-3.0 (2H, m), 3.6-3.7 (1H, m), 3.8-3.9 (1H, m), 3.85 (3H, s), 4.3-4.5 (3H, m), 4.7-4.8 (1H, m), 4.9 (1H, m), 5.0-5.04 (1H, m), 6.53-6.65 (2H, m), 6.8-7.3 (9H, m), 7.5 (1H, d, J = 8Hz), 7.89 (1H, br s), 8.08 (1H, d, J = 8Hz), 8.4 (1H, m), 9.23 (1H, s)
 (24) IR (Nujol) : 3230, 1640, 1610, 1515 cm⁻¹
 30 NMR (DMSO-d₆, δ) : 1.7-1.9 (1H, m), 1.9-2.3 (1H, m), 2.6-3.1 (5H, m), 3.7-3.8 (m) and 4.0-4.4 (3H, m), 4.6-5.0 (m) and 5.3-5.4 (1H, m), 6.5-6.7 (2H, m), 6.8-7.1 (2H, m), 7.1-7.3 (3H, m), 7.3-7.8 (2H, m), 8.0-8.2 (2H, m), 8.44 (d, J = 8Hz) and 8.58 (d, J = 8Hz)(1H), 8.7-8.8 (1H, m), 13.49 (s) and 13.71 (s)(1H)
 (25) IR (Nujol) : 3230, 1640, 1610, 1515 cm⁻¹
 35 NMR (DMSO-d₆, δ) : 1.7-1.9 (1H, m), 1.9-2.3 (1H, m), 2.7-3.2 (5H, m), 3.8-3.8 (m) and 4.0-4.4 (m)(3H), 4.6-5.0 (m) and 5.3-5.4 (m)(4H), 7.0-7.5 (8H, m), 7.5-7.7 (2H, m), 8.0-8.2 (2H, m), 8.5-8.8 (2H, m), 13.50 (s) and 13.74 (s)(1H)
 (26) IR (Nujol) : 3400-3000, 1640-1610, 1340, 750 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.7-1.9 (1H, m), 1.9-2.3 (1H, m), 2.7-3.2 (5H, m), 3.8-3.8 (m) and 4.0-4.4 (m)(3H), 4.6-5.0 (m) and 5.3-5.4 (m)(4H), 7.0-7.5 (8H, m), 7.5-7.7 (2H, m), 8.0-8.2 (2H, m), 8.5-8.8 (2H, m), 13.50 (s) and 13.74 (s)(1H)
 (27) IR (Nujol) : 3420, 3300, 1745, 1680, 1635, 1605, 1570, 1535 cm⁻¹
 40 NMR (DMSO-d₆, δ) : 1.7-2.1 (2H, m), 1.88 (s) and 1.90 (s)(3H), 2.8-3.1 (2H, m), 3.2-3.4 (2H, m), 3.8-4.0 (7H, m), 4.1-4.9 (4H, m), 4.9-5.1 (2H, m), 7.0-7.4 (13H, m), 7.50 (1H, d, J = 8Hz), 7.85 (1H, s), 8.01 (1H, m)
 (28) IR (Nujol) : 3350 (broad), 1635, 1525 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.8-2.1 (2H, m), 2.71 (s) and 2.79 (s)(3H), 2.7-3.1 (2H, m), 3.8-3.7 (1H, m), 3.9-4.1 (1H, m), 4.2-4.7 (4H, m), 4.8-5.1 (2H, m), 6.8-7.4 (11H, m), 7.47 (1H, t, J = 8Hz), 8.14 (1H, d, J = 8Hz), 8.44 (2H, br s), 8.82 (1H, br d)
 (29) IR (Nujol) : 3250, 1640, 1580, 1510, 1285 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.7-2.2 (2H, m), 2.73 and 2.80 (3H, s), 2.8-3.1 (2H, m), 3.2-3.8 (2H, m), 4.1-5.2 (8H, m), 6.3-7.4 (15H, m), 8.4 and 8.85 (1H, m), 9.2 (2H, br)
 (30) IR (Nujol) : 3400-3300, 2800, 2450, 1640, 1600 cm⁻¹
 45 NMR (DMSO-d₆, δ) : 1.7-2.2 (2H, m), 2.74 and 2.79 (3H, s), 2.7-3.0 (2H, m), 2.88 (3H, s), 3.04 (3H, s), 3.5-3.9 (2H, m), 4.2-4.8 (4H, m), 4.7-5.0 (2H, m), 6.5-7.8 (16H, m), 8.4 and 7.9 (1H, m)
 (31) mp : 167-180 °C
 IR (Nujol) : 3440, 3280, 3120, 1680, 1640, 1605, 1575, 1480 cm⁻¹
 50 NMR (DMSO-d₆, δ) : 1.8-1.9 (1H, m), 1.8-2.1 (1H, m), 2.70 (s) and 2.83 (s)(3H), 2.8-3.1 (2H, m), 3.8-4.0 (2H, m), 3.85 (3H, s), 4.2-4.4 (4H, m), 4.85 (1H, t, J = 8Hz), 4.8-5.1 (1H, m), 6.8-7.0 (m) and 7.0-7.4 (m)(11H), 7.49 (1H, d, J = 8Hz), 7.9 (1H, br s), 8.05 (1H, d, J = 8Hz), 8.3-8.5 (1H, m)
 (32) mp : 148-147 °C
 IR (Nujol) : 3460, 3280, 3250, 3100, 1680, 1645, 1605, 1575, 1535, 1415 cm⁻¹

NMR (DMSO-d₆, δ) : 1.7-1.9 (1H, m), 1.9-2.1 (1H, m), 2.72 (s) and 2.88 (s)(3H), 2.8-3.1 (2H, m), 3.5-3.7 (1H, m), 3.8-4.1 (1H, m), 3.85 (3H, s), 4.2-4.5 (2H, m), 4.6-4.8 (2H, m), 4.9-5.1 (2H, m), 6.87 (1H, d, J=7Hz), 7.0-7.8 (11H, m), 7.91 (1H, br s), 8.06 (1H, d, J=7Hz), 8.4-8.6 (1H, m)
 (33) mp : 206-207 °C

5 IR (Nujol) : 3430, 3300, 3120, 1860, 1635, 1615, 1575, 1535, 1250 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.7-1.9 (1H, m), 1.9-2.1 (1H, m), 2.70 (s) and 2.78 (s)(3H), 2.9-3.1 (2H, m), 3.6-3.7 (2H, m), 3.85 (3H, s), 4.2-4.6 (2H, m), 4.6-4.8 (2H, m), 4.8-5.1 (2H, m), 6.8-7.4 (11H, m), 7.48 (1H, d, J=7Hz), 7.88 (1H, s), 8.05 (1H, d, J=7Hz), 8.4-8.6 (1H, m)
 (34) mp : 70 °C - (dec.)

10 IR (Nujol) : 3350, 1840, 1805, 1530, 1495, 1430 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.7-2.0 (3H, m), 2.0-2.2 (1H, m), 2.72 (s) and 2.81 (s)(3H), 2.9-3.1 (2H, m), 3.7-4.0 (5H, m), 4.3-4.7 (3H, m), 4.9-5.1 (1H, m), 7.0-7.4 (12H, m), 7.47 (1H, d, J=8Hz), 7.88 (1H, broad s), 8.08 (1H, d, J=8Hz), 8.3-8.5 (1H, m)

15

Example 45

The object compounds were obtained according to a similar manner to that of Example 27.

(1) IR (Nujol) : 3430, 3200, 1720, 1672, 1635, 1605, 1580, 1537, 1195 cm⁻¹
 20 NMR (DMSO-d₆, δ) : 2.8-3.0 (4H, m), 2.89 (3H, s), 4.3-4.6 (2H, m), 4.7-5.1 (2H, m), 8.9-7.3 (12H, m), 7.3-7.5 (1H, m), 7.8-8.2 (4H, m), 11.5 (1H, s), 12.1 (1H, br s)
 (2) IR (Nujol) : 3300, 1720 (sh), 1630 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.3-2.8 (2H, m), 2.75-3.0 (2H, m), 2.71 and 2.89 (3H, s), 3.56 (2H, s), 4.2-4.72 (3H, m), 4.8-5.0 (1H, m), 6.8-7.4 (15H, m), 7.55 (1H, d, J=7.8Hz), 8.2-8.3 (1H, m), 8.4-8.6 (1H, m), 10.91 (1H, s)

25

Example 46

The object compounds were obtained according to a similar manner to that of Example 28.

30 (1) IR (Nujol) : 3250, 1860 (sh), 1840, 1830, 1540 cm⁻¹
 NMR (DMSO-d₆, δ) : 1.5-2.2 (4H, m), 1.24 (8H, s), 2.5-3.0 (4H, m), 2.71 and 2.78 (3H, s), 4.0-4.6 (3H, m), 4.8-5.0 (2H, m), 6.81 (1H, s), 6.8-7.5 (15H, m), 7.8-8.2 (5H, m), 11.80 (1H, s)
 (2) mp : 238-240 °C (dec.)
 IR (Nujol) : 3380, 3300, 3280 (sh), 3200 (sh), 1685, 1640, 1620, 1545 cm⁻¹
 35 NMR (DMSO-d₆, δ) : 0.88 (3H, d, J=6Hz), 2.72 and 2.75 (3H, s), 2.8-3.1 (4H, m), 3.8-4.2 (3H, m), 4.3-4.6 (2H, m), 4.7-5.1 (3H, m), 6.8-7.4 (13H, m), 7.48 (1H, d, J=8Hz), 7.5-7.9 (3H, m), 8.3 (1H, m), 8.6 (1H, m), 11.58 (1H, s)
 (3) IR (Nujol) : 3280, 1645 (sh), 1630, 1545 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.74 and 2.83 (3H, s), 2.7-3.1 (4H, m), 3.2-3.85 (8H, m), 4.37 and 4.52 (2H, ABq, 40 J=15Hz), 4.8-5.0 (2H, m), 7.0-7.4 (13H, m), 7.48 (1H, d, J=8Hz), 7.85 (1H, d, J=8Hz), 8.2-8.3 (1H, m), 8.5-8.8 (1H, m), 11.88 (1H, s)
 (4) mp : 135-140 °C
 IR (Nujol) : 3250, 1870, 1630, 1605 (sh), 1535, 1210 cm⁻¹
 NMR (DMSO-d₆, δ) : 0.87 (3H, d, J=6Hz), 2.71 and 2.77 (3H, s), 2.5-3.0 (4H, m), 3.8-4.2 (2H, m), 4.3-4.5 (2H, m), 4.8-5.1 (3H, m), 6.8-7.3 (15H, m), 7.3-7.5 (1H, m), 7.8-7.8 (1H, m), 7.8-8.3 (4H, m)

50

Elemental Analysis. Calculated for C ₃₄ H ₃₈ N ₄ O ₆ · 1H ₂ O :	
Found :	C 63.34, H 6.25, N 13.03 C 63.74, H 6.10, N 13.15

55 (5) IR (Nujol) : 3380, 3330, 3240, 3100, 1682, 1640, 1605, 1510, 1200 cm⁻¹
 NMR (DMSO-d₆, δ) : 2.5-2.85 (4H, m), 2.73 and 2.78 (3H, s), 3.63 (2H, d, J=5Hz), 4.2-4.6 (2H, m), 4.75-5.1 (2H, m), 6.85-7.6 (14H, m), 7.9-8.3 (5H, m)
 (6) mp : 218-219 °C
 IR (Nujol) : 3320, 3180, 3080, 1690, 1670, 1630, 1545 cm⁻¹

NMR (DMSO-d₆, δ) : 1.031 (3H, d, J=6Hz), 2.4-3.0 (4H, m), 2.72 and 2.74 (3H, s), 3.35 (1H, s), 4.11 (2H, m), 4.28-5.0 (5H, m), 6.9-7.4 (17H, m), 7.66-7.8 (1H, m), 8.1-8.3 (2H, m), 10.87 (1H, s)

5 Example 47

The object compounds were obtained according to a similar manner to that of Example 5.

(1) IR (Nujol) : 3400, 3300, 1660, 1630 cm⁻¹

10 NMR (DMSO-d₆, δ) : 1.7-2.4 (2H, m), 2.60 (s), 2.72 (s) and 2.78 (s)(3H), 2.8-3.2 (2H, m), 3.6-4.2 (2H, m), 4.2-4.8 (4H, m), 4.8-5.1 (1H, m), 5.1-5.2 (1H, m), 6.8-7.3 (10H, m), 7.3-7.8 (2H, m), 7.9-8.1 (3H, m), 8.5-8.8 (1H, m)

15 Elemental Analysis. Calculated for
C₂₁H₃₁N₃O₄S :

Found :	C 68.74, H 5.77, N 7.78
	C 68.57, H 5.68, N 7.77

20 (2) mp : 97-100 °C

IR (Nujol) : 3310, 1650, 1620, 1545 cm⁻¹

25 NMR (DMSO-d₆, δ) : 2.73 (s) and 2.80 (s)(3H), 2.8-3.1 (2H, m), 3.5-3.8 (2H, m), 4.4-4.8 (3H, m), 4.8-5.1 (2H, m), 6.84 (1H, d, J=16Hz), 7.0-7.3 (10H, m), 7.4-7.5 (4H, m), 7.55-7.65 (2H, m), 8.1-8.2 (1H, m), 8.41 (1H, t, J=8Hz)

30 Elemental Analysis. Calculated for
C₂₅H₃₁N₃O₄·H₂O :

Found :	C 69.17, H 6.80, N 8.34
	C 69.15, H 6.59, N 8.43

35 (3) IR (Nujol) : 3300, 1625, 1515 cm⁻¹

38 NMR (DMSO-d₆, δ) : 0.8-1.0 (6H, m), 1.7-2.2 (4H, m), 2.7-3.0 (6H, m), 3.4-3.7 (2H, m), 4.2-4.8 (4H, m), 4.7-5.1 (2H, m), 6.84 (2H, d, J=8Hz), 6.9-7.2 (4H, m), 7.2-7.4 (3H, m), 8.2-8.3 (m) and 8.6-8.7 (m)(1H), 9.22 (1H, s)

(4) IR (Nujol) : 3300, 1625, 1190, 1080 cm⁻¹

NMR (DMSO-d₆, δ) : 0.88 (s), 1.06 (s), 1.07 (s) and 1.10 (s)(9H), 2.6-2.9 (1H, m), 2.77 (s) and 2.79 (s) (3H),

40 3.0-3.3 (1H, m), 3.06 (s) and 3.11 (s)(3H), 3.3-3.5 (2H, m), 4.1-5.1 (3H, m), 5.5-5.7 (1H, m), 6.73 (1H, d, J=16Hz), 6.8-7.5 (10H, m), 8.1-8.4 (1H, m)

(5) IR (Nujol) : 3300, 1630 cm⁻¹

NMR (DMSO-d₆, δ) : 1.8-1.9 (1H, m), 1.9-2.1 (1H, m), 2.66 (s), 2.72 (s) and 2.80 (s)(3H), 2.8-3.1 (2H, m), 3.2-3.3 (1H, m), 3.6-3.8 (1H, m), 4.2-4.8 (4H, m), 4.8-5.1 (2H, m), 6.9-7.4 (11H, m), 7.4-7.6 (4H, m), 8.44 (1H, d, J=8Hz)

45

Example 48

50 The object compounds were obtained according to a similar manner to that of Example 29.

(1) NMR (DMSO-d₆, δ) : 1.2-2.0 (6H, m), 2.57 and 2.72 (3H, s), 2.8-3.25 (4H, m), 4.0-4.7 (3H, m), 4.75-5.4 (2H, m), 4.86 (2H, s), 7.85-7.4 (21H, m), 7.8-8.2 (3H, m), 9.65 (1H, s)

(2) IR (Nujol) : 3430, 3270, 1715, 1620, 1550 cm⁻¹

NMR (DMSO-d₆, δ) : 1.3-1.75 (4H, m), 2.71 and 2.80 (3H, s), 2.8-3.2 (4H, m), 4.3-4.6 (3H, m), 4.98 (2H, s),

55 4.8-6.1 (1H, m), 6.9-7.5 (17H, m), 7.87 (1H, d, J=8Hz), 8.0-8.35 (3H, m), 11.54 (1H, s)

(3) IR (Nujol) : 3200, 1840, 1515 cm⁻¹

NMR (DMSO-d₆, δ) : 1.7-1.9 (1H, m), 1.9-2.1 (1H, m), 2.7-3.1 (5H, m), 3.6-3.7 (1H, m), 3.8-4.1 (1H, m), 4.30 (1H, br s), 4.5-5.0 (4H, m), 6.85 (2H, d, J=8Hz), 6.8-7.3 (5H, m), 7.46 (1H, d, J=8Hz), 7.6-7.7 (1H, m), 7.87

(2H, br d), 8.00 (1H, d, $J = 8$ Hz), 8.3-8.5 (1H, m), 8.68 (1H, d, $J = 5$ Hz), 11.74 (1H, s)

(4) IR (Nujol) : 3230, 1640, 1525, 1445 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.6-1.8 (1H, m), 1.8-2.1 (1H, m), 2.7-3.2 (5H, m), 3.8-3.7 (1H, m), 3.8-4.1 (1H, m), 4.28 (1H, br s), 4.5-4.7 (2H, m), 4.7-5.1 (2H, m), 7.0-7.5 (10H, m), 7.5-7.7 (1H, m), 7.87 (2H, br s), 8.00 (1H, d, $J = 8$ Hz), 8.45 (1H, br d, $J = 8$ Hz), 8.68 (1H, d, $J = 5$ Hz), 11.79 (1H, s)

Example 48

10 The object compounds were obtained according to a similar manner to that of Example 30.

(1) IR (Nujol) : 3250, 1630, 1525 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.05-1.70 (6H, m), 2.50-3.10 (4H, m), 2.72 (s) and 2.77 (s)(3H), 3.53 (1H, d, $J = 15$ Hz), 3.82 (1H, d, $J = 15$ Hz), 4.20-4.40 (1H, m), 4.43 (s) and 4.46 (s)(2H), 4.80-5.05 (1H, m), 6.90-7.40 (14H, m), 7.58 (1H, d, $J = 8$ Hz), 8.02 (4H, br s), 8.42 (1H, d, $J = 8$ Hz), 10.93 (1H, s)

15 (2) IR (Nujol) : 3200, 1625, 1535, 1205 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.5-1.9 (4H, m), 2.70 and 2.78 (3H, s), 2.7-3.1 (4H, m), 4.4-4.7 (3H, m), 4.8-5.1 (1H, m), 6.9-7.5 (14H, m), 7.8-8.5 (6H, m), 11.78 (1H, s)

Example 50

The object compounds were obtained according to a similar manner to that of Example 31.

(1) The product was used in the next reaction without purification.

(2) IR (Nujol) : 3280, 1630, 1535 cm^{-1}

25 NMR (DMSO- d_6 , δ) : 1.2-1.5 (4H, m), 1.38 (9H, s), 1.5-1.8 (2H, m), 2.20 (2H, t, $J = 7$ Hz), 2.72 (s) and 2.81 (s)(3H), 2.8-3.2 (6H, m), 4.3-4.8 (3H, m), 4.8-5.1 (1H, m), 6.7-6.8 (1H, m), 7.0-7.4 (12H, m), 7.4-7.5 (1H, m), 7.7-7.9 (2H, m), 8.1-8.2 (2H, m), 8.37 (1H, d, $J = 8$ Hz), 11.80 (1H, s)

(3) IR (Nujol) : 3280, 1630, 1535 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.1-1.5 (4H, m), 1.37 (9H, s), 1.5-1.8 (2H, m), 2.72 (s) and 2.81 (s)(3H), 2.8-3.1 (4H, m),

30 3.49 (2H, d, $J = 8$ Hz), 4.3-4.8 (3H, m), 4.8-5.1 (1H, m), 6.87 (1H, t, $J = 8$ Hz), 6.9-7.4 (12H, m), 7.44 (1H, d, $J = 7$ Hz), 7.7-7.9 (2H, m), 8.1-8.2 (2H, m), 8.38 (1H, d, $J = 8$ Hz), 11.80 (1H, s)

(4) IR (Nujol) : 1680, 1640, 1630, 1545 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.1-1.7 (8H, m), 1.19 (6H, t, $J = 7$ Hz), 2.5-3.3 (12H, m), 2.72 (s) and 2.77 (s)(3H), 3.4-3.7 (2H, m), 4.2-4.5 (3H, m), 4.8-5.0 (1H, m), 6.8-7.4 (14H, m), 7.55 (1H, d, $J = 8$ Hz), 7.99 (1H, d, $J = 8$ Hz),

35 8.1-8.2 (1H, m), 8.40 (1H, d, $J = 8$ Hz), 10.27 (1H, s), 10.91 (1H, s)

(5) NMR (CDCl₃, δ) : 1.32 (3H, d, $J = 8$ Hz), 1.41 (9H, s), 1.4-2.0 (4H, m), 2.67 and 2.81 (3H, s), 2.10 (1H, s), 2.85-3.15 (4H, m), 3.7-4.1 (1H, m), 4.1-4.75 (5H, m), 4.85-5.25 (3H, m), 5.78 (1H, d, $J = 8$ Hz), 6.9-7.4 (12H, m), 7.7-8.2 (3H, m), 8.85 (1H, br s)

(6) IR (Nujol) : 3280, 1730, 1640, 1525 cm^{-1}

40 NMR (DMSO- d_6 , δ) : 1.8-2.1 (3H, m), 2.1-2.3 (2H, m), 2.3-2.5 (1H, m), 2.68 (s) and 2.73 (s)(3H), 2.7-3.2 (2H, m), 3.3-3.8 (1H, m), 3.8-4.8 (8H, m), 4.8-5.1 (1H, m), 5.01 (s) and 5.03 (s)(2H), 5.11 (2H, s), 6.9-7.5 (24H, m), 7.7-7.9 (1H, m), 7.99 (1H, d, $J = 7$ Hz), 8.0-8.1 (1H, m), 8.58 (1H, t, $J = 7$ Hz), 11.88 (1H, s)

(7) IR (Nujol) : 3280, 1725, 1640, 1525 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.8-2.1 (3H, m), 2.3-2.5 (3H, m), 2.67 (s) and 2.72 (s)(3H), 2.7-3.1 (2H, m), 3.4-3.8 (1H,

45 m), 3.8-4.8 (8H, m), 4.8-4.5.1 (1H, m), 4.98 (s) and 5.00 (s)(2H), 5.08 (2H, s), 6.9-7.0 (2H, m), 7.0-7.4 (20H, m), 7.45 (2H, d, $J = 8$ Hz), 7.79 (1H, s), 8.00 (1H, d, $J = 8$ Hz), 8.2-8.3 (1H, m), 8.5-8.6 (1H, m), 11.85 (1H, s)

Example 51

50 The object compounds were obtained according to a similar manner to that of Example 32.

(1) mp : 133-137 °C

IR (Nujol) : 3280, 1620, 1545, 1215 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.0 (3H, d, $J = 8$ Hz), 1.3-1.8 (4H, m), 1.89 (3H, s), 2.70 and 2.77 (3H, s), 2.8-3.2 (4H, m), 3.8-4.25 (3H, m), 4.3-4.8 (2H, m), 4.71 (1H, d, $J = 8$ Hz), 4.8-5.1 (1H, m), 6.9-7.8 (15H, m), 8.0-8.35 (4H, m), 11.8 (1H, br)

(2) IR (Nujol) : 3250, 1645, 1520 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.3-1.6 (2H, m), 1.7-2.1 (2H, m), 2.79 (s) and 2.89 (s)(3H), 2.9-3.3 (3H, m), 3.8-3.7 (1H,

m), 3.8-4.1 (1H, m), 4.35-4.65 (2H, m), 4.72 (1H, d, $J=3$ Hz), 4.9-5.1 (2H, m), 7.0-7.4 (12H, m), 7.44 (1H, d, $J=7$ Hz), 7.7-7.9 (2H, m), 8.1-8.2 (1H, m), 11.53 (1H, s)
 (3) mp : 167-169 °C
 IR (Nujol) : 1645, 1585, 1550, 1520 cm^{-1}
 6 NMR (DMSO- d_6 , δ) : 1.4-2.2 (4H, m), 2.8-3.4 (8H, m), 3.8-3.9 (2H, m), 4.2-4.8 (2H, m), 4.8-5.1 (1H, m), 5.3-5.6 (1H, m), 6.7-7.5 (13H, m), 7.8-7.8 (1H, m), 7.8-8.1 (1H, m), 11.46 (1H, br s)

10

Elemental Analysis. Calculated for $\text{C}_{32}\text{H}_{34}\text{N}_4\text{O}_3$:	
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Found :	C 73.54, H 6.58, N 10.72, C 73.32, H 6.59, N 10.58
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18

(4) mp : 175 °C (dec.)

IR (Nujol) : 3300, 1695, 1675, 1630, 1600, 1570, 1530 cm^{-1}
 NMR (DMSO- d_6 , δ) : 1.5-1.9 (3H, m), 1.9-2.1 (1H, m), 2.5-3.1 (4H, m), 3.4-3.8 (4H, m), 4.4-4.8 (3H, m), 5.0-5.1 (1H, m), 7.0-7.3 (11H, m), 7.41 (1H, d, $J=8$ Hz), 7.80 (1H, s), 8.0-8.1 (1H, m), 8.2-8.4 (1H, m), 11.81 (1H, s)

20

28

Elemental Analysis. Calculated for $\text{C}_{32}\text{H}_{32}\text{N}_4\text{O}_3 \cdot 3/4\text{C}_2\text{H}_5\text{OH}$:	
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Found :	C 72.47, H 6.63, N 10.09 C 72.14, H 6.53, N 10.05
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Example 52

30 The object compounds were obtained according to a similar manner to the former half of Example 32.
 (1) NMR (DMSO- d_6 , δ) : 1.2-1.8 (6H, m), 2.4-2.8 (2H, m), 2.72 (s) and 2.81 (s)(3H), 2.8-3.1 (6H, m), 4.4-4.8 (3H, m), 4.8-5.1 (1H, m), 7.0-7.4 (12H, m), 7.46 (1H, d, $J=8$ Hz), 7.8-8.1 (4H, m), 8.1-8.3 (3H, m), 8.40 (1H, d, $J=8$ Hz), 11.75 (1H, s)
 (2) NMR (DMSO- d_6 , δ) : 1.2-1.8 (6H, m), 2.72 (s) and 2.81 (s)(3H), 2.8-3.2 (4H, m), 3.4-3.8 (2H, m), 4.3-4.8 (3H, m), 4.8-5.1 (1H, m), 7.0-7.4 (12H, m), 7.4-7.5 (1H, m), 7.83 (1H, d, $J=8$ Hz), 8.0-8.3 (5H, m), 8.39 (1H, d, $J=8$ Hz), 8.4-8.8 (1H, d), 11.73 (1H, s)

Example 53

40 The object compounds were obtained according to a similar manner to that of Example 18.
 (1) IR (Nujol) : 3300, 3400, 1885, 1640, 1600, 1500 cm^{-1}
 NMR (DMSO- d_6 , δ) : 2.8-2.9 (1H, m), 2.78 (s) and 2.79 (s)(3H), 3.0-3.3 (1H, m), 3.09 (s) and 3.12 (s)(3H), 3.5-3.8 (2H, m), 4.2-4.7 (2H, m), 4.8-5.1 (2H, m), 5.58 (1H, t, $J=7$ Hz), 6.9-7.9 (15H, m), 8.38 (1H, d, $J=8$ Hz)
 (2) IR (Nujol) : 3300, 1625, 1480 cm^{-1}
 NMR (DMSO- d_6 , δ) : 2.8-2.9 (1H, m), 2.75 (s) and 2.78 (s)(3H), 3.0-3.3 (1H, m), 3.08 (s) and 3.11 (s)(3H), 3.4-3.7 (2H, m), 4.1-4.7 (2H, m), 4.8-5.1 (2H, m), 5.57 (1H, t, $J=7$ Hz), 6.74 (1H, d, $J=18$ Hz), 6.9-7.6 (16H, m), 8.22 (1H, d, $J=8$ Hz)
 (3) IR (Nujol) : 3300, 1730, 1610, 1530 cm^{-1}
 50 NMR (DMSO- d_6 , δ) : 1.7-1.9 (1H, m), 2.1-2.3 (1H, m), 2.71 and 2.78 (3H, s), 2.8-3.1 (2H, m), 3.8-4.0 (2H, m), 4.01 (2H, s), 4.21 (1H, m), 4.43 (2H, s), 4.68 (1H, m), 4.97 (1H, m), 5.12 (2H, s), 7.0-7.3 (12H, m), 7.46 (1H, d, $J=7.8$ Hz), 7.85 (1H, s), 8.07 (1H, d, $J=7.4$ Hz), 8.45 (1H, m)

58 Example 54

The object compounds were obtained according to a similar manner to the latter half of Preparation 20.
 (1) IR (Neat) : 1640, 1620, 1535 cm^{-1} NMR (DMSO- d_6 , δ) : 1.00 (s), 1.02 (s), 1.05 (s), 1.09 (s), 1.10

(s) and 1.12 (s)(9H), 2.6-2.9 (1H, m), 2.78 (s), 2.78 (s) and 2.81 (s)(3H), 3.07 (s), 3.11 (s) and 3.14 (s)(3H), 3.1-3.7 (3H, m), 3.80 (s), 3.82 (s) and 3.84 (s)(3H), 4.1-5.0 (2H, m), 5.0-5.2 (1H, m), 5.5-5.8 (1H, m), 6.8-7.4 (12H, m), 7.4-7.6 (1H, m), 7.7-8.0 (1H, m), 8.0-8.2 (1H, m), 8.10 (1H, s)

(2) IR (Nujol) : 3440, 1670, 1640, 1600, 1500 cm^{-1}

5 NMR (DMSO-d₆, δ) : 0.98 (s) and 1.11 (s)(9H), 2.7-2.9 (1H, m), 2.78 (s) and 2.81 (s)(3H), 3.0-3.3 (1H, m), 3.09 (s) and 3.13 (s)(3H), 3.4-3.7 (2H, m), 4.22 (d) and 4.29 (d)(J = 14.5Hz, 1H), 4.71 (d) and 4.78 (d)(J = 14.5Hz, 1H), 4.9-5.1 (1H, m), 5.61 (1H, t, J = 7Hz), 6.8-7.8 (12H, m), 7.6-7.9 (2H, m), 7.84 (1H, s), 8.32 (d) and 8.39 (d)(J = 8Hz, 1H)

10

Elemental Analysis. Calculated for $\text{C}_{34}\text{H}_{39}\text{N}_3\text{O}_5$:	
Found :	C 71.68, H 6.90, N 7.38 C 71.61, H 6.87, N 7.25

15

20 Example 55

The object compound was obtained according to a similar manner to that of Example 19.

IR (Nujol) : 3350, 1630, 1615, 1530, 1175, 900 cm^{-1}

25 NMR (DMSO-d₆, δ) : 1.9-2.1 (1H, m), 2.1-2.4 (1H, m), 2.31 (3H, s), 2.68 (s) and 2.73 (s)(3H), 2.7-3.1 (2H, m), 3.7-4.1 (2H, m), 3.83 (3H, s), 4.40 (2H, s), 4.7-5.0 (2H, m), 5.1-5.2 (1H, m), 6.8-7.4 (14H, m), 7.51 (1H, d, J = 8Hz), 7.72 (2H, d, J = 8Hz), 7.79 (1H, s), 8.00 (1H, d, J = 8Hz), 8.55 (1H, br s)

30 Example 56

35 The object compounds were obtained according to a similar manner to that of Example 38.

(1) IR (Nujol) : 3230, 1625, 1525 cm^{-1}

NMR (DMSO-d₆, δ) : 1.7-2.1 (3H, m), 2.2-2.5 (3H, m), 2.67 (s) and 2.74 (s)(3H), 2.7-3.1 (2H, m), 3.5-3.7 (2H, m), 4.0-4.8 (4H, m), 4.8-4.8 (1H, m), 4.8-5.1 (1H, m), 6.8-7.4 (12H, m), 7.45 (1H, d, J = 7Hz), 7.82 (1H, s), 8.00 (1H, d, J = 8Hz), 8.4-8.7 (1H, m), 8.7-8.9 (1H, m), 11.73 (1H, s)

38

(2) IR (Nujol) : 3400, 1625, 1540 cm^{-1}

NMR (DMSO-d₆, δ) : 2.6-2.9 (1H, m), 2.74 (s) and 2.79 (s)(3H), 3.0-3.3 (1H, m), 3.12 (s) and 3.15 (s)(3H), 3.4-3.8 (2H, m), 3.84 (3H, s), 4.2-4.8 (2H, m), 4.9-5.2 (2H, m), 5.58 (1H, t, J = 6Hz), 6.8-7.3 (12H, m), 7.50 (1H, d, J = 8Hz), 7.78 (1H, d, J = 8Hz), 8.08 (1H, s), 8.12 (1H, d, J = 8Hz)

40

Example 57

The object compound was obtained according to a similar manner to that of Example 22.

IR (Nujol) : 3200, 1630, 1525 cm^{-1}

45 NMR (DMSO-d₆, δ) : 1.8-2.0 (1H, m), 2.3-3.2 (3H, m), 2.68 (s) and 2.72 (s)(3H), 2.83 (3H, s), 3.5-4.3 (3H, m), 4.40 (2H, br s), 4.5-5.1 (2H, m), 6.8-7.55 (14H, m), 7.80 (1H, s), 7.9-8.1 (1H, m), 8.4-8.7 (1H, m), 11.62 (1H, s)

50

Example 58

The object compound was obtained according to a similar manner to that of Example 38.

IR (Nujol) : 3220, 1880, 1840, 1630, 1525 cm^{-1}

55 NMR (DMSO-d₆, δ) : 1.22 (8H, t, J = 7Hz), 1.7-1.9 (1H, m), 2.3-3.3 (14H, m), 4.0-4.8 (4H, m), 4.8-4.8 (1H, m), 4.8-5.1 (1H, m), 6.8-7.4 (12H, m), 7.46 (1H, d, J = 7Hz), 7.80 (1H, s), 7.89 (1H, d, J = 8Hz), 8.4-8.7 (2H, m), 10.39 (1H, br s), 11.77 (1H, s)

Example 59

The object compound was obtained according to a similar manner to that of Example 40.

IR (Nujol) : 3200, 1630 (sh), 1600, 1525 cm^{-1}

5 NMR (DMSO- d_6 , δ) : 1.75-1.9 (1H, m), 2.1-2.3 (1H, m), 2.69 and 2.77 (3H, s), 2.9-3.1 (2H, m), 3.59 (2H, s), 3.8-4.0 (2H, m), 4.23 (1H, m), 4.42 (2H, s), 4.69 (1H, m), 4.96 (1H, m), 7.0-7.3 (12H, m), 7.47 (1H, d, J = 7.4Hz), 7.89 (1H, s), 8.08 (1H, d, J = 7.3Hz), 8.45 (1H, m)

10 Example 60

The object compound was obtained according to a similar manner to that of Example 41.

IR (Nujol) : 3400, 1600, 1530 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 1.83 (1H, m), 2.18 (1H, m), 2.70 and 2.77 (3H, s), 2.9-3.1 (2H, m), 3.58 (2H, s), 3.91 (2H, br), 4.18 (1H, m), 4.4-4.75 (5H, m), 4.96 (1H, m), 6.9-7.4 (13H, m), 7.87 (1H, br s), 8.04 (1H, m), 8.45 (1H, br)

20 Example 61

The object compound was obtained according to a similar manner to that of Preparation 4.

IR (Nujol) : 3300, 1640, 1530 cm^{-1}

25 NMR (DMSO- d_6 , δ) : 1.75-1.9 (1H, m), 2.08-2.2 (1H, m), 2.65 and 2.71 (3H, s), 2.8-3.5 (4H, m), 3.8-3.8 (3H, m), 4.25-4.8 (4H, m), 4.8-5.08 (2H, m), 6.4 (2H, br), 6.95-7.4 (14H, m), 8.59 (d, J = 7.7Hz) and 9.03 (d, J = 7.7Hz) (1H)

Example 62

30 The object compound was obtained according to a similar manner to the latter half of Example 32.

IR (Nujol) : 3300, 1720, 1630, 1538 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.3-1.8 (4H, m), 2.3-2.5 (4H, m), 2.69 and 2.78 (3H, s), 2.9-3.3 (4H, m), 4.4-4.7 (3H, m), 4.85-5.2 (1H, m), 6.95-7.5 (13H, m), 7.7-7.9 (2H, m), 8.1-8.45 (3H, m), 11.8 (1H, s), 12 (1H, br)

35 Example 63

40 To an ice-cooled solution of Starting Compound (0.45 g) in methanol (45 ml) was added 1N sodium hydroxide (0.75 ml) solution. The solution was stirred for two hours at room temperature. After concentration, the product was extracted with ethyl acetate and the organic layer was washed successively with water and sodium chloride solution, and was dried over magnesium sulfate. After evaporation of the solvent, the solid residue was washed with ethyl acetate, filtered and dried to give Object Compound (0.30 g).

mp : 131-136 °C

IR (Nujol) : 3440, 3275, 1720, 1680, 1630, 1605, 1580, 1635 cm^{-1}

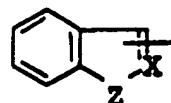
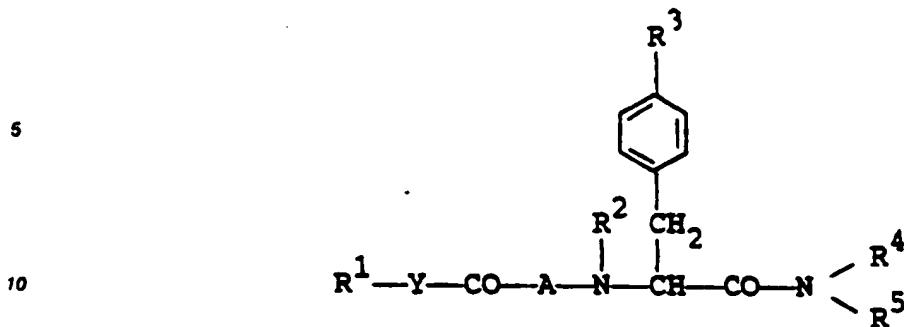
45 NMR (DMSO- d_6 , δ) : 1.7-2.1 (2H, m), 2.8-3.4 (4H, m), 3.5-4.0 (4H, m), 3.85 (3H, s), 4.2-5.2 (7H, m), 6.9-7.4 (12H, m), 7.48 (1H, d, J = 8Hz), 7.88 (1H, s), 8.08 (1H, d, J = 8Hz), 8.38 (1H, s)

Claims

50

1 A compound of the formula :

55



wherein the symbol of a line and dotted line is a single bond or a double bond,
X is CH or N, and

Z is O, S or NH,

each of which may have suitable substituent(s);

R² is hydrogen or lower alkyl;

R³ is hydrogen or hydroxy;

R⁴ is lower alkyl which may have suitable substituent(s), and

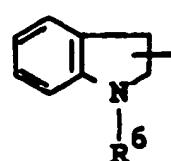
R⁵ is ar(lower)alkyl which may have suitable substituent(s) or pyridyl(lower)alkyl, or

R⁴ and R⁵ are linked together to form benzene-condensed lower alkylene;

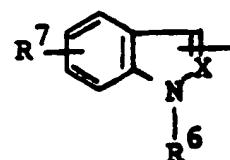
A is an amino acid residue excepting D-Trp, which may have suitable substituent(s); and
Y is bond, lower alkylene or lower alkenylene,
and a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, wherein

R¹ is lower alkyl, aryl which may have one to three substituent(s) selected from hydroxy, lower alkoxy and N,N-di(lower)alkylamino, arylamino, pyridyl, pyrrolyl, pyrazolopyridyl, quinolyl, benzofuryl, benzothienyl, a group of the formula :



wherein R⁶ is hydrogen or esterified carboxy, or a group of the formula :



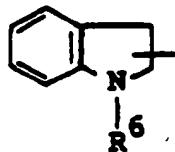
wherein X is CH or N,

R⁶ is hydrogen, lower alkyl, carboxy(lower)alkyl, esterified carboxy(lower)alkyl, N,N-di(lower)alkylamino-(lower)alkyl or N,N-di(lower)alkylamino(lower)alkylcarbamoyl(lower)alkyl and

R⁷ is hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy, N,N-di(lower)alkylamino or acyl,

R² is hydrogen or lower alkyl,
 R³ is hydrogen or hydroxy,
 R⁴ is lower alkyl, hydroxy(lower)alkyl or acyloxy(lower)alkyl,
 R⁵ is ar(lower)alkyl, haloar(lower)alkyl, halo(lower)alkylar(lower)alkyl or pyridyl(lower)alkyl, or
 5 R⁴ and R⁵ are linked together to form benzene-condensed lower alkylenes,
 A is a bivalent residue derived from an amino acid selected from proline, hydroxyproline, glycine, serine, asparagine, aminoisobutyric acid, azetidinecarboxylic acid, thioproline, aspartic acid, lysine, methionine, threonine, alanine, ornithine, hydroxypiperidinecarboxylic acid, 4-acyloxyproline, 4-lower alkoxyproline, 4-carboxy(lower)alkoxyproline, 4-esterified carboxy(lower)alkoxyproline, 4-lower alkythioproline, 4-aminoproline, 4-acylaminoproline, O³-lower alkylserine, O³-ar(lower)alkylserine, thioproline sulfoxide, thioproline sulfone, O⁴-ar(lower)alkyl hydrogen aspartate, (carbamoyl and hydroxy substituted lower alkylamino)- β -aspartate, carbamoyl(lower)alkylamino- β -aspartate, morpholino- β -aspartate, (carbamoyl and lower alkylcarbamoyl substituted lower alkylamino)- β -aspartate, N⁶-acetylysine, N⁶-acetylornithine, and
 Y is bond, lower alkylenes or lower alkenylene.
 15 3. A compound of claim 2, wherein
 R¹ is lower alkyl, aryl which may have one to three substituent(s) selected from hydroxy, lower alkoxy and N,N-di(lower)alkylamino, arylamino, pyridyl, pyrrolyl, pyrazolopyridyl, quinolyl, benzofuryl, indazolyl, benzothienyl, a group of the formula :

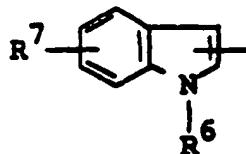
20



25

wherein R⁶ is hydrogen or lower alkoxy carbonyl, or a group of the formula :

30



35

wherein R⁶ is hydrogen, lower alkyl, carboxy(lower)alkyl, lower alkoxy carbonyl(lower)alkyl, N,N-di(lower)-alkylamino(lower)alkyl or N,N-di(lower)alkylamino(lower)alkylcarbamoyl(lower)alkyl, and
 R⁷ is hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or N,N-di(lower)alkylamino or lower alkoxy carbonyl, and

40

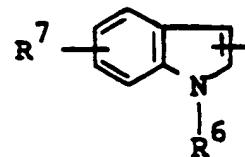
R⁴ is lower alkyl, hydroxy(lower)alkyl or lower alkanoyloxy(lower)alkyl,
 R⁵ is ar(lower)alkyl, haloar(lower)alkyl, halo(lower)alkylar(lower)alkyl or pyridyl(lower)alkyl, or
 R⁴ and R⁵ are linked together to form benzene-condensed lower alkylenes,
 A is a bivalent residue derived from an amino acid selected from proline, 4-hydroxyproline, glycine, serine, asparagine, 2-aminobutyric acid, azetidine-2-carboxylic acid, thioproline, aspartic acid, lysine, methionine, threonine, alanine, ornithine, 5-hydroxypiperidine-2-carboxylic acid, 4-lower alkanoyloxyproline, 4-lower alkanesulfonyloxyproline, 4-arenesulfonyloxyproline, 4-carbamoyloxyproline, 4-lower alkoxyproline, 4-carboxy(lower)alkoxyproline, 4-lower alkoxy carbonyl-lower alkoxyproline, 4-lower alkythioproline, 4-aminoproline, 4-carboxy(lower)alkylamino proline, 4-amino(lower)alkylamino proline, 4-ar(lower)-alkoxy carbonyl amino(lower)alkylamino proline, 4-amino and carboxy substituted lower alkanoyl amino proline, 4-ar(lower)alkoxy carbonyl amino and ar(lower)alkoxy carbonyl substituted lower alkanoyl amino proline, 4-oxalocamino proline, 4-lower alkoxy alaminoproline, 4-lower alkanesulfonylaminoproline, 4-N,N-di(lower)alkylamino(lower)alkylamino proline, O³-lower alkylserine, O³-ar(lower)alkylserine, thioproline sulfoxide, thioproline sulfone, O⁴-ar(lower)alkyl hydrogen aspartate, (carbamoyl and hydroxy substituted lower alkylamino)- β -aspartate, carbamoyl(lower)alkylamino- β -aspartate, morpholino- β -aspartate, (carbamoyl and lower alkylcarbamoyl substituted lower alkylamino)- β -aspartate, N⁶-ar(lower)-alkoxy carbonyl lysine, N⁶-haloar(lower)alkoxy carbonyl lysine, N⁶-N,N-di(lower)alkylamino-lower alkanoyl lysine, N⁶-morpholinocarbonyl lysine, N⁶-N-lower alkoxy carbonyl-N-lower alkoxy carbonyl(lower)alkylamino-lower alkanoyl lysine, N⁶-(hydroxy and lower alkanoyl amino substituted lower alkanoyl)lysine, N⁶-(hydroxy

and lower alkoxy carbonylamino substituted lower alkanoyl)lysine, N^6 -lower alkoxy carbonylamino(lower)-alkanoyllysine, N^6 -amino(lower)alkanoyllysine, N^5 -ar(lower)alkoxy carbonylornithine, N^6 -(hydroxy and lower alkanoyl)amino substituted lower alkanoyl)ornithine, N^5 -(hydroxy and lower alkoxy carbonylamino substituted lower alkanoyl)ornithine.

5 4. A compound of claim 3, wherein

R¹ is indazolyl or a group of the formula :

10

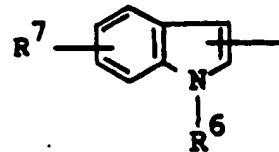


15 wherein R⁶ is hydrogen, lower alkyl, carboxy(lower)alkyl, lower alkoxy carbonyl(lower)alkyl, N,N-di(lower)-alkylamino(lower)alkyl or N,N-di(lower)alkylamino(lower)alkyl carbamoyl(lower)alkyl, and
R⁷ is hydrogen, hydroxy, halogen, lower alkyl, lower alkoxy or N,N-di(lower)alkylamino,
R⁴ is lower alkyl, hydroxy(lower)alkyl or lower alkanoyloxy(lower)alkyl,
R⁵ is phenyl(lower)alkyl, halophenyl(lower)alkyl, halo(lower)alkylphenyl(lower)alkyl or pyridyl(lower)alkyl, and
20 A is a bivalent residue derived from an amino acid selected from proline, 4-hydroxyproline, glycine, serine, asparagine, 2-aminoisobutyric acid, azetidine-2-carboxylic acid, thioproline, aspartic acid, lysine, methionine, threonine, alanine, ornithine, 5-hydroxypiperidine-2-carboxylic acid, 4-lower alkanoyloxyproline, 4-lower alkanesulfonyloxyproline, 4-phenylsulfonyloxyproline, 4-carbamoyloxyproline, 4-lower alkoxyproline, 4-carboxy(lower)alkoxyproline, 4-lower alkoxy carbonyl-lower alkoxyproline, 4-lower alkylthioproline, 4-aminoproline, 4-carboxy(lower)alkanoylaminoproline, 4-amino(lower)alkanoylaminoproline, 4-phenyl(lower)-alkoxy carbonylamino(lower)alkanoylaminoproline, 4-amino and carboxy substituted lower alkanoylaminoproline, 4-phenyl(lower)alkoxy carbonylamino and phenyl(lower)alkoxy carbonyl substituted lower alkanoylaminoproline, 4-oxaloaminoproline, 4-lower alkoxyaminoproline, 4-lower alkanesulfonylaminoproline, 4-N,N-di(lower)alkylamino(lower)alkanoylaminoproline, O³-lower alkylserine, O³-phenyl(lower)alkylserine, thioproline sulfide, thioproline sulfone O⁴-phenyl(lower)alkyl hydrogen aspartate, (carbamoyl and hydroxy substituted lower alkylamino)- β -aspartate, carbamoyl(lower)alkylamino- β -aspartate, morpholino- β -aspartate, (carbamoyl and lower alkyl carbamoyl substituted lower alkylamino)- β -aspartate, N^6 -phenyl(lower)alkoxy carbonyllysine, N^6 -halophenyl(lower)alkoxy carbonyllysine, N^6 -N,N-di(lower)alkylamino-lower alkanoyllysine, N^6 -morpholinocarbonyllysine, N^6 -N-lower alkoxy carbonyl-N-lower alkoxy carbonyl(lower)alkylamino(lower)alkanoyllysine, N^6 -(hydroxy and lower alkanoyl)amino substituted lower alkanoyl)lysine, N^6 -amino(lower)alkanoyllysine, N^5 -phenyl(lower)-alkoxy carbonylornithine, N^5 -(hydroxy and lower alkanoyl)amino substituted lower alkanoyl)ornithine, N^5 -(hydroxy and lower alkoxy carbonylamino substituted lower alkanoyl)ornithine.

25 5. A compound of claim 4, wherein

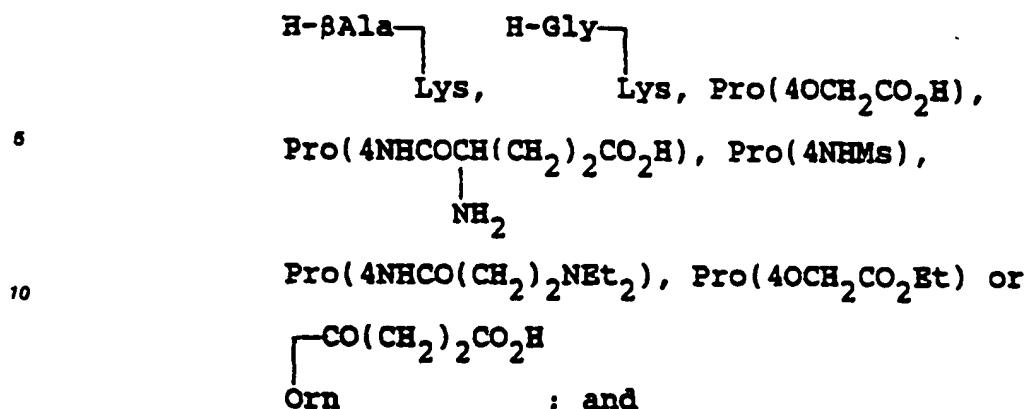
R¹ is Indazolyl or a group of the formula :

45



50 wherein R⁶ is hydrogen, methyl, isopropyl, carboxymethyl, t-butoxycarbonylmethyl, N,N-dimethylaminoethyl or N,N-dimethylaminoethylcarbamoylmethyl, and
R⁷ is hydrogen, hydroxy, chloro, methyl, methoxy or N,N-dimethylamino,
R² is hydrogen or methyl,
R³ is hydrogen or hydroxy,
55 R⁴ is methyl, hydroxyethyl or acetoxyethyl,
R⁵ is benzyl, fluorobenzyl, chlorobenzyl, trifluoromethylbenzyl or pyridylmethyl,

A is Pro, D-Pro, Pro(4OH), Gly, Ser, Asn, Aib, Azt,
 Tpr, Asp, Lys, Met, Thr, Ala, Orn,
 5 Tpr(O), Tpr(O₂), Pro(4OCH₂CO₂Bu^t),
 Pro(4OMs), Pro(4NH₂),
 10 Pro(4NHCOCO₂Et), Pro(4OCONH₂), Asp(OBzl),
 15 Gln-NHBu^t Et₂N(CH₂)₂CO Lys,
 Asp , Lys(Z), Lys,
 20 Boc-Thr Ac-Thr COCH₂N CH₂CO₂Bu^t Boc ,
 Lys, Lys, Lys
 25 Lys , Pro(4OAc), Pro(4NHCOCH₂NH₂),
 Pro(4NHCOCH₂NH₂), Pro(4NHCO(CH₂)₂CHCO₂Bzl),
 NH₂
 30 Pro(4NHCO(CH₂)₂CHCO₂H), Pro(4NHCO(CH₂)₂CO₂H),
 NH₂
 Pro(4NHCOCO₂H), Pro(4OTs), Pro(4SMe), Pro(4OMe),
 35 Ser(Bzl), Lys(Cl-Z), Asp , Asp ,
 Gly-NH₂ Boc-βAla-
 Asp , Ser(Bu^t), Orn(Z), Lys,
 40 Boc-Gly Boc-Thr
 Lys, Orn,
 45 Pro(4NHCOCH₂)₂CO₂Bzl, Ac-Thr-
 NH₂ Orn,
 50



15 Y is bond, methylene, ethylene, trimethylene, or vinylene.

6. A compound of claim 5, wherein

R¹ is indazolyl or imidazolyl.

R² is hydrogen.

20 R³ is hydrogen or hydroxy.

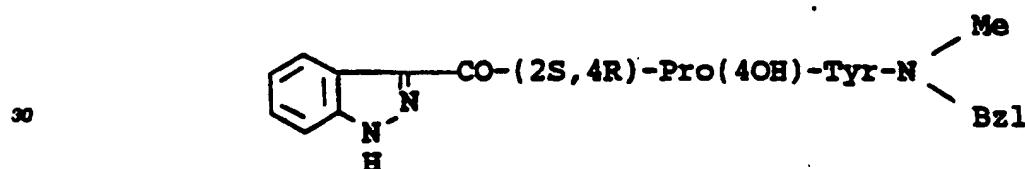
R⁴ is methyl.

R⁵ is benzyl, and

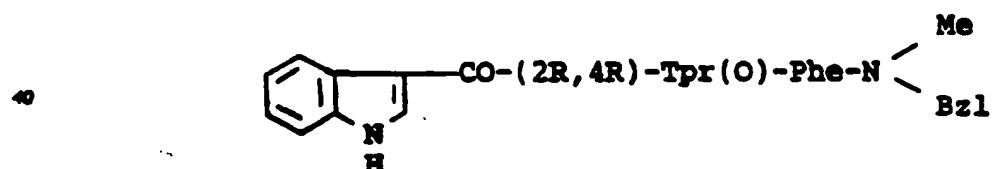
Y is bond.

7. A compound of claim 6, which is selected from the group consisting of :

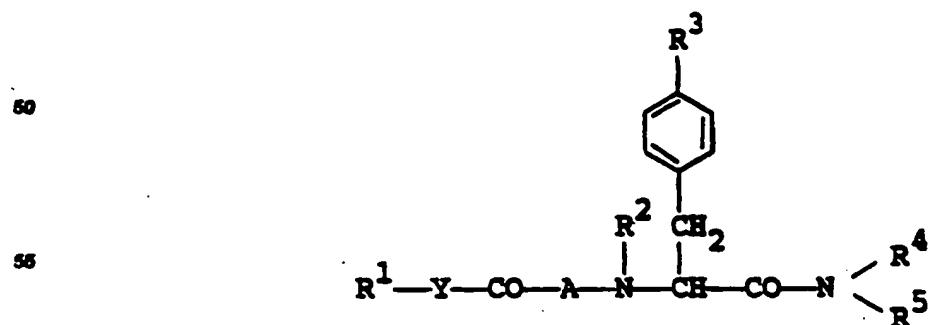
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35 , and

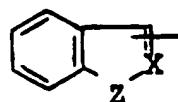


45 8. A process for preparing a compound of the formula :



Wherein R¹ is lower alkyl, aryl, arylamino, pyridyl, pyrrolyl, pyrazolopyridyl, quinolyl, or a group of the formula :

5



10 wherein the symbol of a line and dotted line is a single bond or a double bond,
 X is CH or N, and
 Z is O, S or NH,
 each of which may have suitable substituent(s);
 R² is hydrogen or lower alkyl;
 15 R³ is hydrogen or hydroxy;
 R⁴ is lower alkyl which may have suitable substituent(s), and
 R⁵ is ar(lower)alkyl which may have suitable substituent(s) or pyridyl(lower)alkyl, or
 R⁴ and R⁵ are linked together to form benzene-condensed lower alkylene;
 A is an amino acid residue excepting D-Trp, which may have suitable substituent(s); and
 20 Y is bond, lower alkylene or lower alkenylene,
 or a pharmaceutically acceptable salt thereof, which comprises
 (1) reacting a compound of the formula :

25

30

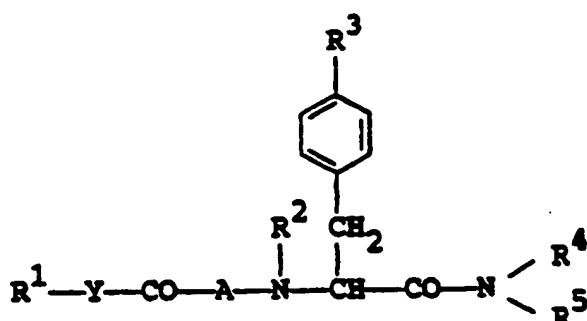
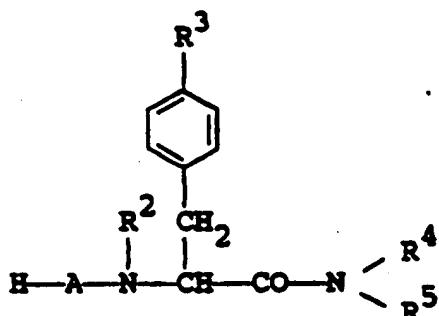
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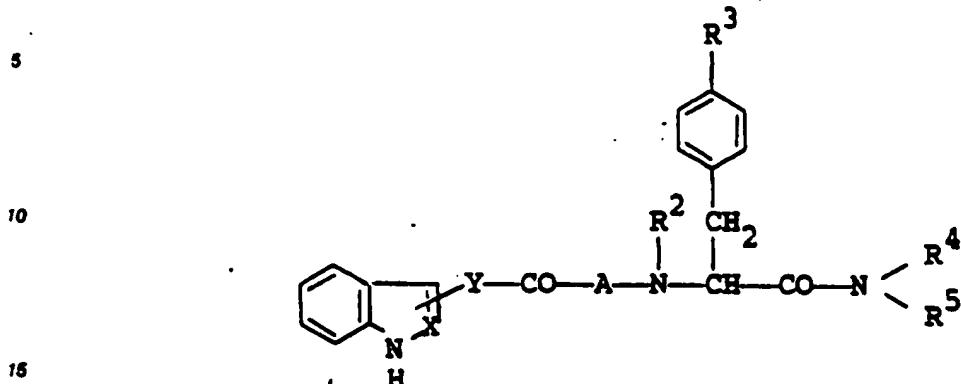
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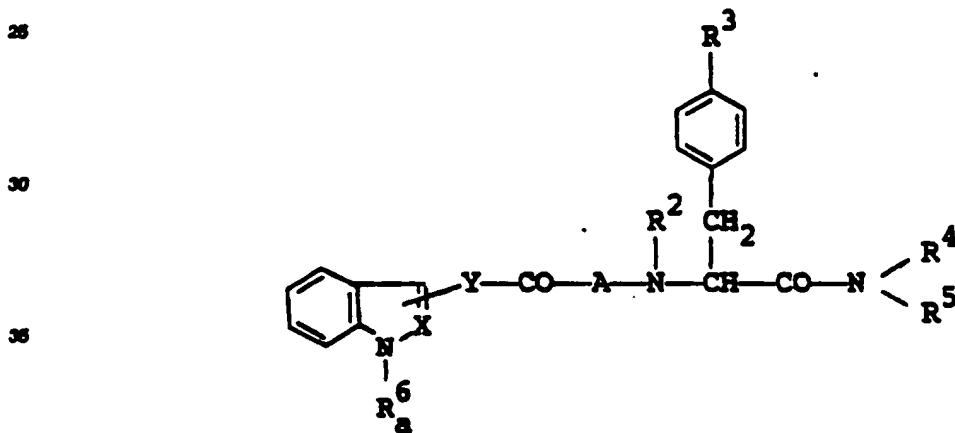
wherein R¹, R², R³, R⁴, R⁵, A and Y are each as defined above,
 or a salt thereof, or

(2) reacting a compound of the formula :



wherein R², R³, R⁴, R⁵, A, X, Y and the symbol of a line and dotted line are each as defined above, or a salt thereof, with a compound of the formula :

20 L - R₆^a wherein R₆^a is lower alkyl which may have suitable substituent(s), and
L is an acid residue,
to give a compound of the formula :



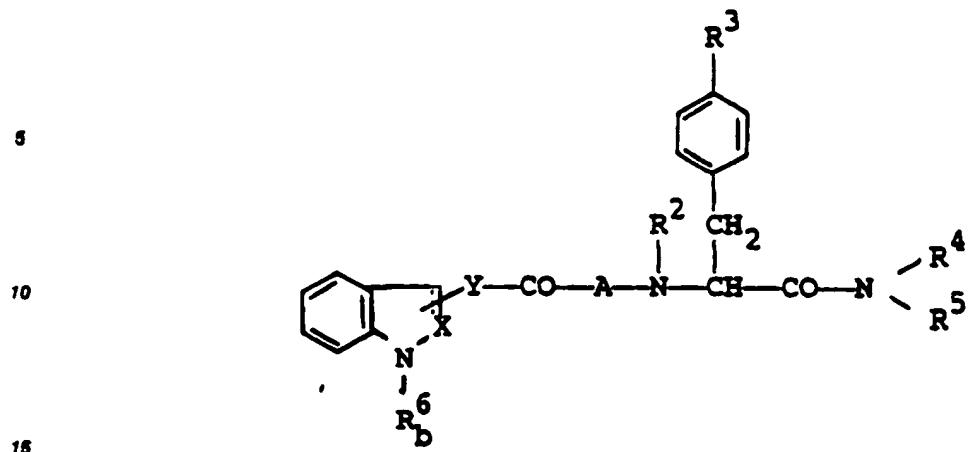
40 wherein R², R³, R⁴, R⁵, R₆^a, A, X, Y and the symbol of a line and dotted line are each as defined above, or a salt thereof, or

(3) subjecting a compound of the formula :

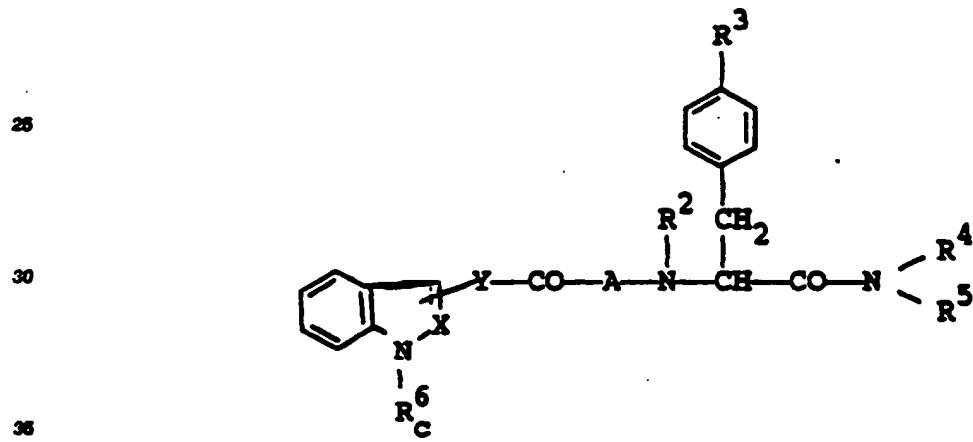
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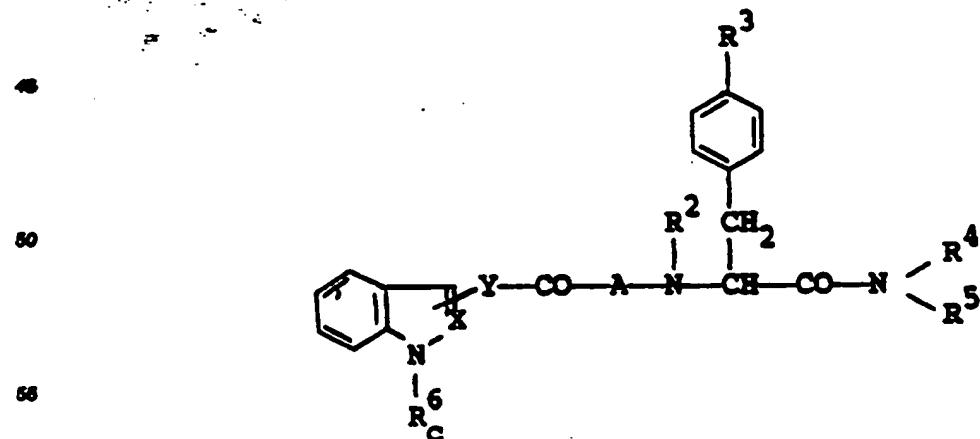


wherein R², R³, R⁴, R⁵, A, X, Y and the symbol of a line and dotted line are each as defined above, and R_b⁶ is protected carboxy(lower)alkyl,
or a salt thereof, to elimination reaction of the carboxy protective group, to give a compound of the formula :



wherein R², R³, R⁴, R⁵, A, X, Y and the symbol of a line and dotted line are each as defined above, and R_c⁶ is carboxy(lower)alkyl,
or a salt thereof, or

40 (4) subjecting a compound of the formula :



wherein R², R³, R⁴, R⁵, A, X, Y, R_c⁶ and the symbol of a line and dotted line are each as defined above, or its reactive derivative at the carboxy group or a salt thereof, to amidation reaction, to give a compound of the formula :

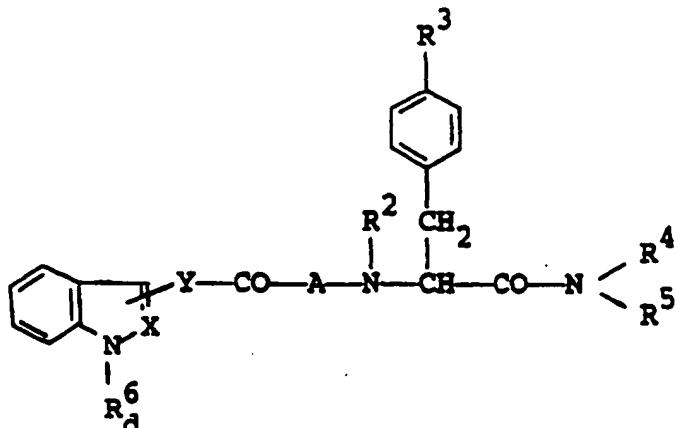
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wherein R², R³, R⁴, R⁵, A, X, Y and the symbol of a line and dotted line are each as defined above, and R_d⁶ is carbamoyl(lower)alkyl which may have suitable substituent(s), or a salt thereof, or

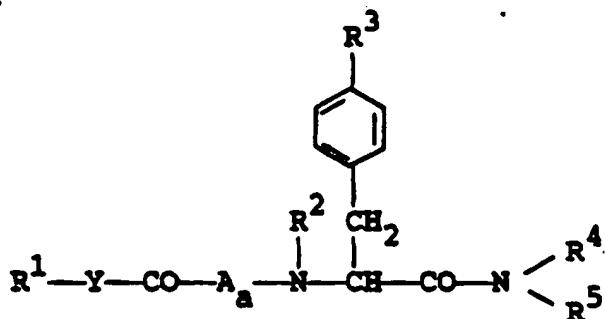
(5) subjecting a compound of the formula :

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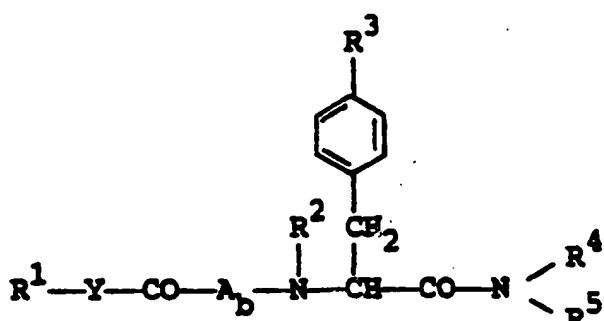
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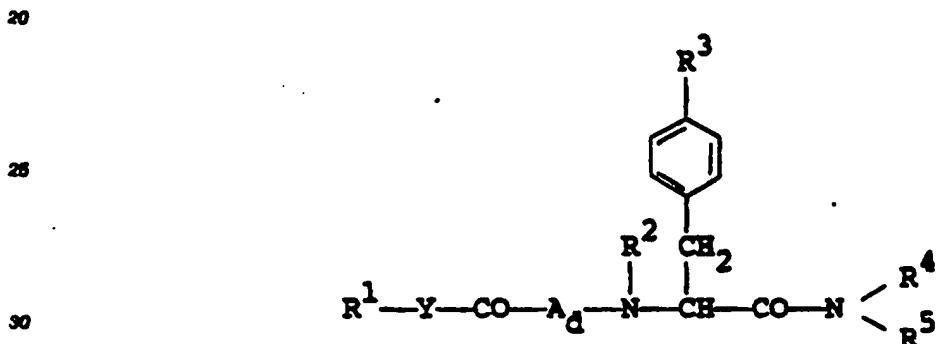
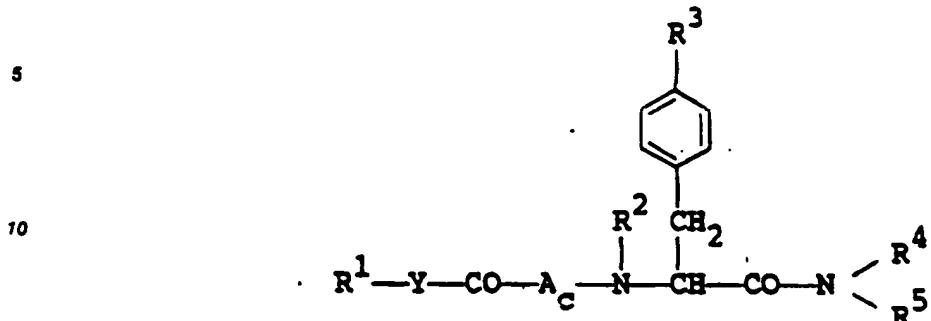
wherein R¹, R², R³, R⁴, R⁵ and Y are each as defined above, and

A_a is an amino acid residue containing a thio, or a salt thereof, to oxidation reaction, to give a compound of the formula :

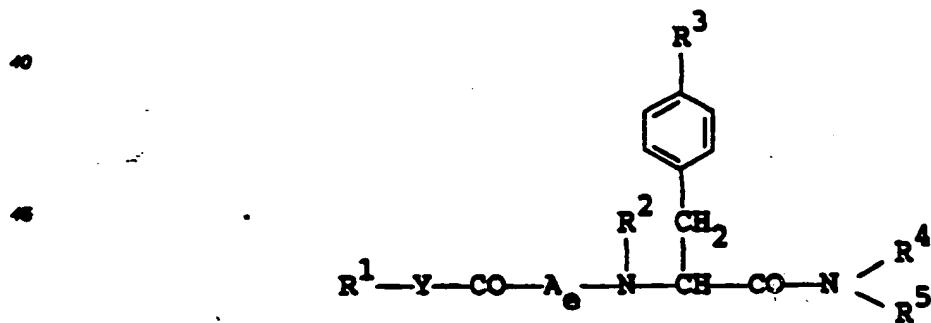


wherein R¹, R², R³, R⁴, R⁵ and Y are each as defined above, and A_b is an amino acid residue containing a sulfinyl or sulfonyl, or a salt thereof, or

(6) subjecting a compound of the formula :



(7) reacting a compound of the formula :



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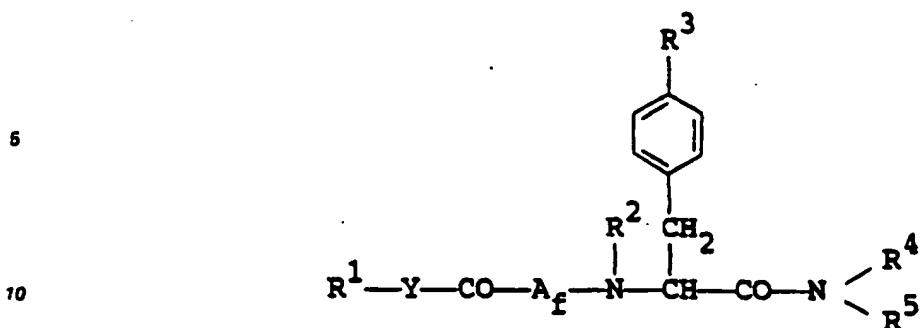
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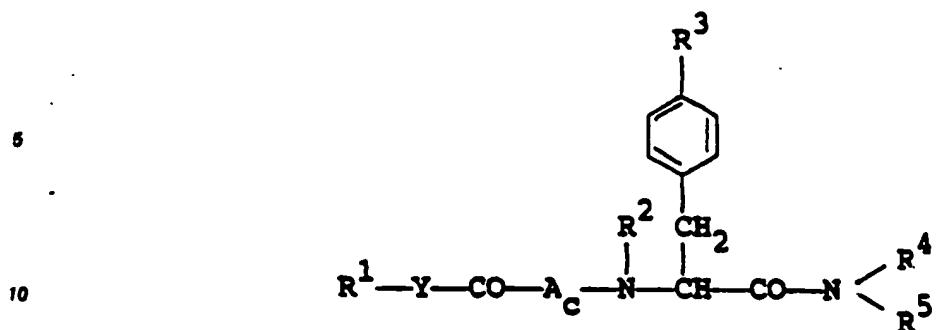
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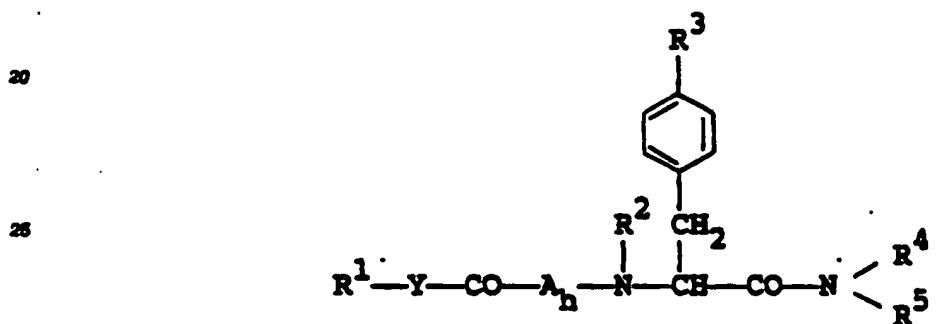




wherein R¹, R², R³, R⁴, R⁵, Y and A_c are each as defined above,

or a salt thereof, or

(9) reacting a compound of the formula :



wherein R¹, R², R³, R⁴, R⁵ and Y are each as defined above, and A_h is an amino acid residue containing a protected hydroxy,

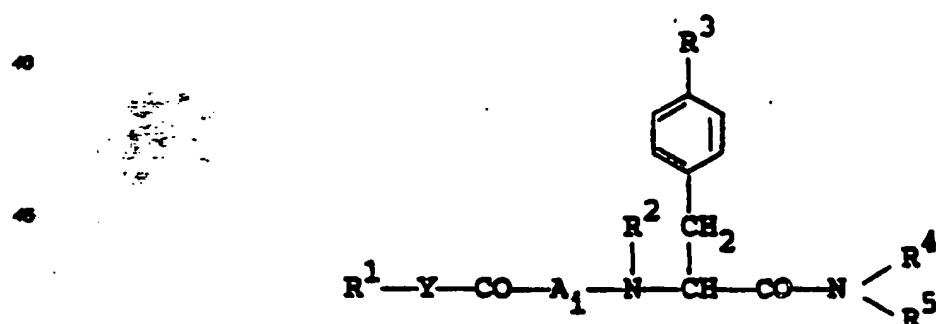
or a salt thereof, with a compound of the formula :

M₆SR⁹

wherein R⁹ is lower alkyl, and

M₆ is an alkaline metal,

to give a compound of the formula :

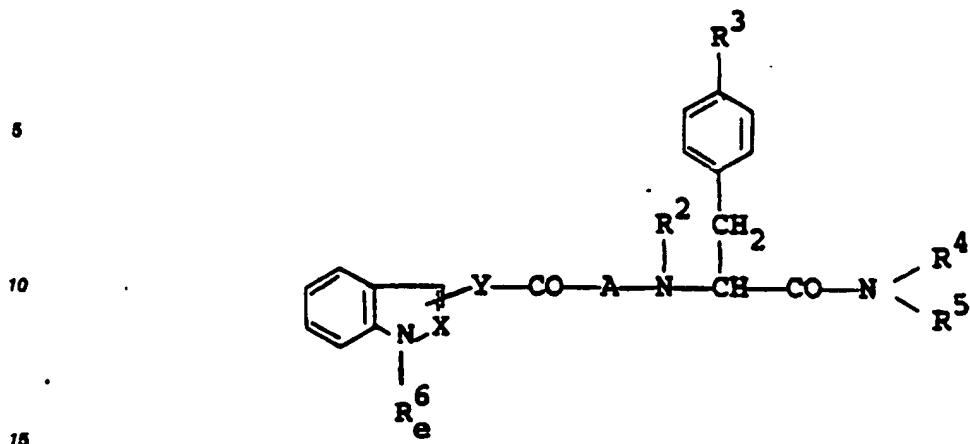


wherein R¹, R², R³, R⁴, R⁵, and Y are each as defined above, and A₁ is an amino acid residue containing lower alkylthio,

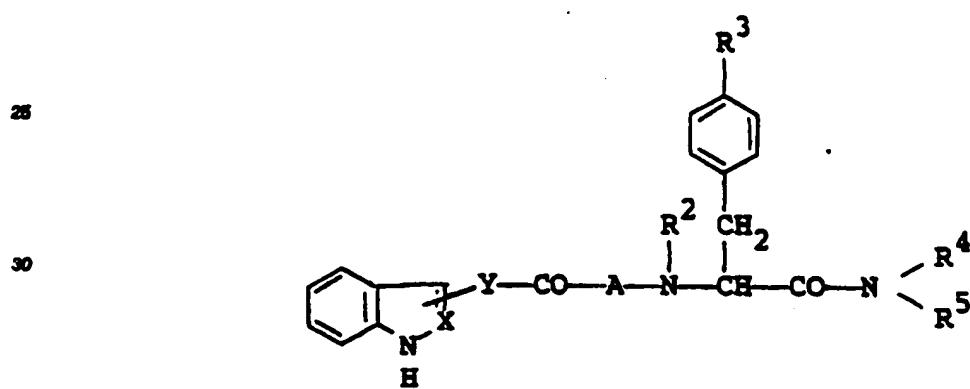
or a salt thereof, or

(10) subjecting a compound of the formula :

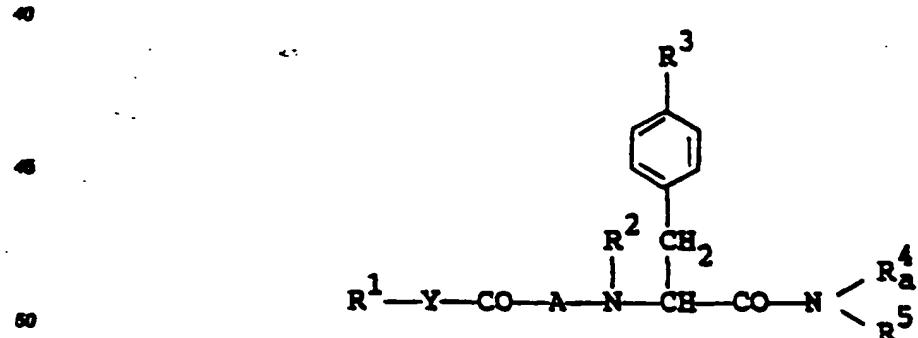
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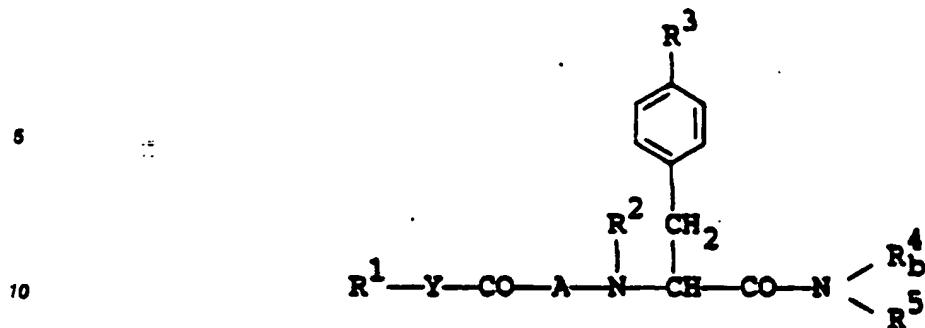
20 or a salt thereof, to elimination reaction of the amino protective group, to give a compound of the formula :



(11) subjecting a compound of the formula :



55 or a salt thereof, to elimination reaction of the hydroxy protective group, to give a compound of the formula



wherein R¹, R², R³, R⁴, A and Y are each as defined above, and
 R_b⁴ is hydroxy(lower)alkyl,
 or a salt thereof.

9. A pharmaceutical composition which comprises a compound of claim 1 and a pharmaceutically acceptable carrier or excipient.
10. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 with a pharmaceutically acceptable carrier or excipient.
11. A compound of claim 1 for use as a medicament.
12. A compound of claim 1 for use as a tachykinin antagonist.
13. A compound of claim 1 for use as a substance P antagonist.
14. A use of a compound of claim 1 for manufacturing a medicament for treating tachykinin mediated diseases.
15. A method for treating tachykinin mediated diseases which comprises administering a compound of claim 1 to human or animals.